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(54) **Nucleotide sequences useful as type-specific probes, PCR primers and LCR probes for the amplification and detection of human papilloma virus, and related kits and methods**

Nukleotid-Sequenzen nützlich als typenspezifische Sonden, PCR Primers und LCR Sonden zur Amplifikation und zum Nachweis von humanem Papillomavirus, sowie dazu verwendete Kits und Verfahren

Séquences nucléotidiques utiles comme sondes spécifiques du type amorces de PCR et sondes pour l'amplification et détection du virus-papilloma humain, et kits et procédés utilisés dans ce but

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Description

This invention relates generally to human papilloma virus, and more particularly, relates to nucleotide sequences of short strands of human papilloma virus which can be amplified and/or used to determine the presence of human papilloma virus products in a test sample, and some of which also can be amplified and/or used to determine the specific type of human papilloma virus of types 16 and 18 present in the test sample.

Human papilloma virus (HPV)) is recognized as a venereally-transmitted disease of the anogenital tract which often is associated with the pathogenesis of cervical cancer and its precursor lesions. More than 56 types of HPV have been characterized. Of these, at least 21 types infect the anogenital tract. L. Gregoire et al., J. Clin. Micro 27 (12): 2660- 2665(1989). These mucosotropic viruses are associated most frequently with benign condyloma or latent infections. However, the presence of HPV in premalignant lesions and invasive cancers, particularly of the cervix, may reflect the oncogenic potential of these viruses. See P. M. Howley, in Important Advances in Oncology, D. T. DeVita, Jr. et al., eds., J. B. Lippincott, Philadelphia, PA (1987) at pages 55-73.

Certain HPV types, namely, HPV type 16 and type 18, and to a lesser extent HPV types 31, 33 and 35, are found in a high proportion of invasive cervical cancers and their metastases. However, many HPV types which infect the anogenital tract, such as HPV types 6 and 11, are found most commonly in benign condyloma and only rarely are found in invasive cancers. HPV detected in the anogenital tract can be classified broadly as low risk papilloma viruses (HPV types 6 and 11), intermediate risk papilloma viruses (HPV types 31 , 33 and 35) or high risk papilloma viruses (HPV types 16 and 18), based on the association of the particular HPV type with malignancy. A. T. Lorincz et al., J Nat'l Cancer Inst. 79:671 (1987). Thus, the detection of the presence of HPV and the determination of the specific type of HPV can provide a diagnostic and prognostic tool useful for determining the clinical significance associated with certain HPV types. The early detection of HPV by sensitive and specific reagents and methodologies also could provide earlier therapeutic management and counseling.

A need therefore exists for accurate and reliable methods to identify and type HPV in clinical specimens. However, known polyclonal antisera prepared by immunizing animals with disrupted virions are capable of detecting HPV antigens in only about 30-70% of cutaneous and mucosal warts. Further, the antisera are broadly cross-reactive. Available immunological tests have two major drawbacks. First, only well-differentiated cells apparently are capable of viral antigen expression. HPV-infected tissues which show higher degrees of neoplasia, such as carcinoma in situ, rarely contain HPV antigen. Thus, the further the development of the malignancy, the smaller the amount of detectable virus in the tested tissue. Secondly, these immunological tests are unable to identify specific viral types.

It is known that papilloma viruses share amino acid sequences in the major capsid proteins. See, for example, C. C. Baker, in The Papovaviridae (Vol. 2), P. M. Howley and N. P. Salzman, eds., Plenum Publ. Corp., New York (1987) at pages 321-385. The DNAs of this virus cross-hybridize, indicating homologous sequences. M. F. Law et al., J. Virol. 58:225-229 (1979). Thus, molecular hybridization techniques have been developed as a more sensitive and specific means of detecting and differentiating HPV DNA and RNA in clinical specimens. See A. T, Lorinez, Obstetrics and Gynecol. Clinics of N. America 14:451 (1987).

Sequences specific for the DNA and RNA of human papilloma virus are known and have been published. See, for example, PCT application No. WO 89/69940 published October 19, 1989, PCT application No. WO 86/05816 published October 9, 1986 and European Patent Application No. 0 301 968 published February 1, 1989.

The molecular hybridization techniques used to detect homologous DNA sequences are sensitive and can be highly specific if used with probes which bind to nucleic acid sequences which are unique to a particular HPV type. However, the concentration of total viral DNA in a given clinical sample may be below the limit of sensitivity of the test. For example, the amount of viral DNA in dysplastic cervical lesions is reduced with increasing dysplasia.

To overcome this problem of sensitivity, viral DNA sequences can be amplified by using, for example, the polymerase chain reaction (PCR) or the ligase chain reaction (LCR) techniques. The products thus obtained can be identified by using conventional hybridization techniques for identification of virus types, such as Southern blotting. See C. Oste, Biotechniques 6:163(1988), K. B. Mullis, U. S. Patent No. 4,683,202, and EP-A-320 308 (BioTechnica).

Both PCR and LCR serve to amplify the DNA present in a test sample to detectable levels. In practice, the level of sensitivity is about 50 to 100 copies per sample. The next most sensitive technique is dot-blot, which can detect about 10,000 molecules, while Southern blot reliably detects about 100,000 copies of DNA per sample.

Thus, the appropriate diagnosis of HPV may require two steps. In one strategy, the presence of a clinically relevant type of HPV is first detected with a group-specific primer. After the presence of HPV is detected, differentiation between types can be performed by using a type-specific probe having low homology between the HPVs of the group. Alternatively, differentiation can be performed using a mixture of type-specific probes at the outset, provided these probes amplify DNA independently of each other, and that they can be detected independently. In the past, such tasks were attempted using specific antibodies. In general, nucleic acid probes and primers allow greater discrimination among subtypes than do antibodies. The use of DNA-based tests increases both sensitivity and specificity over prior-art antibody-based tests.

It therefore would be advantageous to provide oligonucleotide strands of DNA which could be amplified and used to detect the presence, if any, of HPV in a test sample. It also would be advantageous to provide short oligonucleotide strands of DNA which could be amplified and used to detect the presence, if any, of specific types of HPV in the test sample. The combined use of oligonucleotide strands would be advantgeous for allowing for the specific and sensitive in vitro diagnosis of the presence and specific type of HPV present in test samples.

SUMMARY OF THE INVENTION

Oligonucleotides of from about 10 to about 60 nucleotides are provided which can be amplified and used either to detect specific sequences of specific types of human papilloma virus, or consensus regions with high homology among different types. The presence of HPV is determined by contacting the test sample with sequences provided to detect the presence, if any, of HPV types 6, 11, 16, 18, 31, 33 and 61. This may be done with or without prior amplification, for example, by PCR or LCR. Either type-specific or consensus amplification is also possible. Two oligonucleotides are provided if the sequence is to be amplified by PCR, and four oligonucleotides provided if amplification is by LCR, in accordance with these known amplification procedures. After the presence of HPV is detected, the type of HPV present in the sample can be determined by using HPV type-specific probes, by subsequent rounds of PCR, or by LCR. Alternatively, the presence of type-specific HPV can be determined by contacting the test sample directly with type-specific nucleotide sequence provided by the invention for the detection of HPV types 16 and 18. ,.iso provided are methods for using the oligonucleotides and kits for amplifying and detecting the presence of human papilloma virus.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a photograph of a gel following electrophoresis showing the results when the primers PCR 1 and PCR5 were used to amplify selected plasmids wherein HPV 6 is in lane 1, HPV 11 is in lane 2, HPV 16 is in lane 3, HPV 18 is in lane 4, and HPV 31 is in lane 5, HPV 33 is in lane 6, HPV 61 is in lane 7, and molecular weight standards are in lane 8.

FIG. 2 is a photograph of a gel following electrophoresis showing the results when the primers PCR 1, PCR2, PCR3, PCR4 and PCR5 were used to amplify plasmid p65.16.8 (HPV 16). PCR1 and PCR5 are primers according to the invention.

FIG. 3 is a photograph of the ethidium bromide-stained gels wherein PCR 1 4 and PCR15 are used in conjunction with IWDO to obtain amplified PCR product.

FIG. 4 is a graph of results obtained from performing LCR on 10^7 molecules of the selected target using LCR5A, LCR5A', LCR5B and LCR5B'. The rate of reaction of 4-methyl lumbelliferone is expressed as fluorescence counts/second/second and plotted against the target HPV type.

FIG. 5 is a graph of results obtained from performing LCR on 10^7 molecules of the selected target using LCR6A, LCR6A', LCR6B and LCR6B'. The rate of reaction of 4-methyllumbelliferone is expressed as fluorescence counts/second/second and plotted against the target HPV type.

FIG. 6 is a graph of results obtained from perfomring LCR on 10^7 molecules of the selected target using LCR7A, LCR7A', LCR7B and LCR7B'. The rate of reaction of 4-methyllumbelliferone is expressed as fluorescence counts/second/second and plotted against the target HPV type.

FIG. 7 is a graph of results obtained from perfomring LCR on 10^7 molecules of the selected target using LCR8A, LCR8A', LCR8B and LCR8B'. The rate of reaction of 4-methyllumbelliferone is expressed as fluorescence counts/second/second and plotted against the target HPV type.

DETAILED DESCRIPTION OF THE INVENTION

The appropriate diagnosis of HPV requires two sets of conditions. The first enables the detection of all pertinent types, and the second set allows differentiation among them. In the past, such tasks have been attempted using specific antibodies. In general, nucleic acid probes and primers allow greater discrimination among subtypes than do antibodies. Thus, the use of DNA-based tests tends to increase both sensitivity and specificity over antibody-based tests.

U. S. Patents No. 4,683,195 and 4,683,202 teach a method of amplifying DNA sequences by using PCR. This method now is a standard procedure in many molecualr biology laboratories. Examples 1-3 which follow below utilize the procedures taught in these two patents and the method as described in the package insert of the commercially-available Gene-Amp™ kit (Document No. 55635-6/89, Perkin-Elmer/Cetus, Emeryville, CA).

In PCR, two complementary polynucleotide strands are amplified by treating the strands with two oligonucleotide primers such that an extension product of each primer is synthesized which is complementary to each nucleic acid strand. The primers are selected such that the extension product of one primer forms a template for the synthesis of an extension product from the other primer once the extension product of the one primer is separated from the template. A chain reaction is maintained by a cycle of denaturing the primer extension products from their templates, treating

the single-stranded molecule generated with the same primers to re-anneal, and allowing the primers to form further extension products. The cycle is repeated for any many times as it takes to increase the target nucleic acid segments to a concentration where they can be detected.

The amplified target sequence can be detected by any of several known techniques; for example, by denaturing the double-stranded products formed by PCR, and treating those products with one or more reporter probes which hybridize with the extension products. The reporter probe has a detectable label, and usually is added in excess. The unhybridized reporter probe, therefore, must be separated from the hybridized reporter probe by involving a separation step. In another method of detecting the extension products without reporter probe and a separation step, the extension products are detected by gels stained with ethidium bromide. The diagnosis can be confirmed by transferring the DNA to nitrocellulose and probing with a probe specific to the HPV type suspected of being present in the sample.

Alternately with PCR, one may take advantage of known restriction sites within the HPV DNA to demonstrate that the amplified DNA contains the expected sequence by examining the cleavage pattern(s) generated with one or more restriction endonucleases. Verifying the authenticity of the amplified sequence may be necessary for two reasons: (1) to ensure that sequences complementary to the amplifying primers are not fortuitously present in cellular DNA which does not contain HPV DNA, and (2), to identify the type of HPV present in the sample. If the sequences chosen for amplification are conserved among HPV types, then the finding of an amplified product does not implicate a particular HPV type. It also should be possible to predict the size of the amplified product based on the binding positions of the two primers. Thus, when that product is found, one reasonably can be assured that HPV is present. However, two different types of HPV may give the same or different size products. Thus, hybridization should be used to confirm the identity of the amplified sequence until confidence is built that the interpretation of the results is reliable. It should be pointed out that the PCR technique will identify only closely related, or type-specific sequences in the absence of highly homologous primers, since only a small portion of the genome is analyzed.

Another particularly useful detection technique is described in EP-A-357 011. In this method, a different reporter molecule, e.g. hapten, is attached to each primer. Following amplification, but before denaturation, duplexes can be detected by "capturing" one hapten (hapten1) with a solid phase coated with anti-hapten1. The separated complex can be detected with a conjugate of label and anti-hapten2, and label associated with the solid phase can be measured.

The Ligase Chain Reaction (LCR) amplifies sections of DNA by copying the section of DNA, and copying the copies of that section of DNA, many times over. This method is described in European Patent Application No. 0 320 308 published June 14, 1989, which is incorporated herein by reference. In this procedure, two probes (for example, A and B) complementary to immediately adjacent regions of a target sequence are hybridized and ligated. This ligated probe then is denatured away from the target, after which it is hybridized with two additional probes (A' and B') of sense opposite to the initial probes A and B. The secondary probes are themselves then ligated. Subsequent cycles of denaturation/hybridization/ligation create the formation of double-length probes of both sense (+) and antisense (-).

In LCR, the nucleic acid of the sample is provided either as single stranded DNA or as double-stranded DNA which is denatured to separate the strands. Four probes are utilized: the first two probes (A and B) are the so-called primary probes, and the second two probes (A' and B') are the so-called secondary probes. The first probe (A) is a single strand capable of hybridizing to a first segment of the primary strand of the target nucleotide sequence. The second probe (b) is capable of hybridizing to a second segment of the primary strand of the target nucleotide sequence. The 5' end of the first segment of the primary strand of the target is positioned relative to the 3' end of the second segment of the primary strand of the target to enable joining of the 3' end of the first probe to the 5' end of the second probe, when the probes are hybridized to the primary strand of the target nucleotide sequence. The third probe (A') is capable of hybridizing to the first probe, and the fourth probe (B') is capable of hybridizing to the second probe (B). The hybridized probes are ligated to form reorganized fused probe sequences. Then, the DNA in the sample is denatured to separate ligated probes from sample DNA. Successive cycles wherein the ligated probes and target DNA undergo the above-described process are performed to increase the amount of detectable DNA in the sample. The amount of cycles performed is dependent upon the sequence used and the sensitivity required of the test. Usually, the cycle can be repeated from 15 to 60 times. At least one of the probes can be conjugated to a signal generating compound.

If the four probes are conjugated to appropriate binding members, the detection of amplified product can be accomplished using standard manual or automated immunoassay procedures known to those skilled in the art. These procedures include, for example, immunochromatography, ELISA, EIA and MEIA. Hybridization also can be accomplished by following standard dot-, slot- or replica-blot procedures which are known to those in the art. The sequences can be labelled with an appropriate signal generating compound (label), which is capable of generating a measureable signal detectable by external means. The various signal generating compounds contemplated include chromogens, catalysts such as enzymes, luminescent compounds such as fluoroscein and rhodamine, chemiluminescent compounds, radioactive elements such as ^{32}P, and other labels known to those of ordinary skill in the art. The selection of a particular label is not critical, but it will be capable of producing a a signal either by itself or in conjunction with one or more additional substances. A variety of different indicator reagents can be formed of label and specific binding member. Either the label or a specific binding member can be varied. Examples of specific binding members which

can be used as a member of the indicator reagent include antibodies, both monoclonal, polyclonal, and fragments thereof; avidin or biotin, biotin and anti-biotin, a carbohydrate or a lectin, a complementary nucleotide sequence, an effector or a receptor molecule, an enzyme cofactor or an enzyme; an enzyme inhibitor or an enzyme; also any antigenic substances, haptens, antibodies, and combinations thereof.

The test sample can be any biological material suspected of containing HPV. Thus, the test sample can be human body tissue, or a test sample which contains cells suspected of containing HPV.

The invention will now be described by way of Examples, which are meant to describe, but not to limit, the spirit and scope of the invention.

The following terms used in the examples are trademarks, tradenames or chemical abbreviations as specified:

TRIS - chemical abbreviation for [tris(hydroyxmethyl)aminomethane], used as a buffer.
EDTA - chemical abbreviation for ethylenediaminetetraacetic acid, a chelating agent.
FITC - chemical abbreviation for fluorescein isothiocyanate, a flourescent hapten derivative.
NHS-ester - chemical abbreviation for N-hydroxysuccinamide ester
MES - chemical abbreviation for [2-(N-morpholino)ethanesulfonic acid], a buffer.
TWEEN®-20 - trademark of Atlas Chemical for polyoxyethylene sorbitan monolaurate, a detergent.
BIS-TRIS - chemical abbbreviation for [bis-(2-hydroxyethyl)-amino]tris-(hydroxymethyl)methane, a buffer.
TRITON X- 100® - trademark of Rohm & Haas for nonaethylene glycol octylphenol ether, a detergent.
IMx® - trademark of Abbott Laboratories for an automated instrument for performing microparticle enzyme immunoassay (MEIA).

EXAMPLES

EXAMPLE 1

PCR was performed essentially following the package insert of the commercially available Gene-Amp™ kit (document No. 55635-6/89, available from Perkin-Elmer/Cetus, Emeryville, CA). The following reagents were mixed in a 0.5 mL polypropylene tube and used in performing PCR:

Reagent	Final Concentration
Water	(to give final volume = 50 or 100 µL)
Reaction Buffer	10 mM TRIS pH 8.3
	50 mM KC1
	1.5 mM MgC12
	0.01% gelatin
dNTP mixture	200 µM each of dATP,dCTP,dGTP, and TTP
pCR1	1 µM
pCR2	1 µM
plasmid	10 µL 1 ng/100µL
(or control-human placental DNA (Pooled Placental DNA, catalog D-3287, Sigma Chemical Co, St. Louis MO).	
DNA polymerase, Thermus Acquaticus	25 *or* 63.9 units/1 mL

After mixing, the reaction mixture was overlayed with 100 µL of mineral oil. The tube then was placed in an instrument capable of incubation at several temperatures, and subjected to 30 or 40 cycles of programmed temperature change. The precise cycle of temperature change used, and the instrument used, varied with the experiment, and is detailed in the descriptions of the figures in Example 3.

EXAMPLE 2

Following the procedure of Example 1, the following sequences were found to amplify sections of papilloma virus types 6, 11, 16, 18, 31, 33, and 61 using PCR.

PCR1: CAGATGTCTC TGTGGCGGCC TAGTG (ID No. 1)

PCR5: AGGTGTCAGG AAAACCAAAT TTATT (ID No. 5)

PCR14: GAATTAGTTA GACCATTTAA AAG (ID No. 6)

PCR15: GGGGAAACAC CAGAATGGAT A (ID No. 7)

IWDO: ATCATATGCC CACTGTACCA T (ID No. 8)

Sequence IWDO is derived from a sequence disclosed in International application number PCT/US86/00629 (WO 86/05816).

TABLE 1 shows the sequences and where they map to to in the various types.

TABLE 1

SEQUENCES WHICH CAN BE USED AS PROBES OR PCR PRIMERS

PROBE	SEQ ID No.	SEQUENCE	SENSE	MAPS TO: (type 6)	MAPS TO: (type 11)	MAPS TO: (type 16)	MAPS TO: (type 18)	MAPS TO: (type 31)	MAPS TO: (type 33)
PCR1:	1	CAGATGTCTCTGTGGCGGCCTAGTG	+	5786-5810	5768-5792	5634-5658	5610-5634	5550-5574	5591-5615
PCR2:	2	CGTTTTCCATATTTTTTTGCAGATG	+	5767-5791	5749-5773	615-5639	5591-5615	5531-5555	5572-5596
PCR3:	3	AAGTTGTAAGCACCGATGAATATGT	+	5844-5868	5826-5850	695-5719	5671-5695	5611-5635	5652-5676
PCR4:	4	AATGTACCCTAAATACCCTATATTG	-	6008-5984	5990-5966	865-5841	5841-5817	5784-5760	5825-58C1
PCR5:	5	AGGTGTCAGGAAAACCAAATTTATT	-	6044-6020	6026-6002	5901-5877	5877-5853	5820-5796	5861-5837
PCR14:	6	GAATTAGTTAGACCATTTAAAAG	+	1495-1517	1495-1517	1524-1546	1595-1617	1462-1484	1518-1540
PCR15:	7	GGGGAAACACCAGAATGGATA	+	1834-1854	1834-1854	1863-1883	1934-1954	1801-1821	1857-1877
IWDO:	8	ATCATATGCCCACTGTACCAT	-	1931-1911	1931-1911	1960-1940	2031-2011	1898-1878	1954-1934

note: PCR2, PCR3 and PCR4 are not probes or PCR primers of the invention

EXAMPLE 3

Linearized plasmids containing full-length papilloma virus inserts in pGEM3 were used as targets. These were pHPV6.1 (HPV6), pSP65.11.5 (HPV 11), p65.16,8 (HPV16), pHPV18H(HPV18), pG3 HPV31 (HPV31), pLNK322.HPV33 (HPV33), and pBR322.HPV61 (HPV61). The Programmable Cyclic Reactor™ (available from Ericomp, San Diego) was used as the incubation instrument. Following PCR procedures as described in Example 1,10 µL aliquots were analyzed by electrophoresis through agarose (comprising a 5:3 ratio of NuSieve®:SeaKem® GTG, available from the FMC Corp., Rockland, ME) in a buffer comprising 0.089 M TRIS, 0.089 M borate, 2 mM EDTA, and 0.5 ppt ethidium bromide.

FIG. 1 is a photograph of an ethidium bromide-stained 1.2% agarose gel showing results using 63.9 units/mL DNA polymerase, in the DNA Thermal Cycler™ (Perkin-Elmer/CETUS, Emeryville, CA). The samples were heated for 5 minutes at 94°C, then subjected to 40 cycles of a temperature program of: 1 minute at 94°C, 2 minutes at 40°C, and 1.5 minutes at 72°C. The PCR primers used in this case were PCR 1 and PCR5 of Example 2. Examination of the gel following electrophoresis showed bands at the expected positions, i.e. 292 bp. Lane 1, HPV6; lane 2, HPV 11; lane 3, HPV16 ; lane 4, HPV 18; lane 5, HPV31; lane 6, HPV33, lane 7, HPV61; lane 8, pooled human placental DNA (suspected of having HPV infection); lane 9, molecular weight markers-Hae III digest of ΦX174.

FIG. 2 is a photograph of an ethidium bromide-stained 4% agarose gel showing results using 25 units/mL DNA polymerase, in the Programmable Cycler Reactor™ (Ericomp, San Diego, CA). Samples in this case were subjected to 30 cycles of a temperature program of: 50°C for one (1) minute, 72°C for two (2) minutes and 95°C for one (1)) minute. In this case, the primers PCR1 , PCR2, PCR3, PCR4 and PCR5 of Example 2 were used to amplify plasmid

p65,16,8(HPV 16). Examination of the gel of Figure 2 shows bands at the expected positions, i.e., PCR 1 and PCR4, 235 bp, lane 2; PCR1 and PCR5, 267 bp, lane 4; PCR2 and PCR4, 254 bp, lane 6; PCR2 and PCR5, 286 bp, lane 8; PCR3 and PCR4, 174 bp, lane 10; PCR3 and PCR5, 206 bp, lane 12; molecular weight marker, 123, 246, 369, 492,... bp ladder, lane 1. Note footnote to Table 1.

FIG. 3 is a photograph of an ethidium bromide-stained 1.2% agarose gel showing results using the same conditions as FIG. 1. In this case, PCR14 and PCR15 were used as primers in conjunction with IWDO. The expected size of the amplified PCR product of PCR 14 and IWDO is 437 bp for all of the HPV types tested. The expected size of the product of PCR 15 and IWDO is 98 bp. Products of these sizes appear in the gels, confirming that PCR14 and PCR15, used in conjunction with IWDO, will amplify HPV DNA of types 6, 11, 16, 18, 31 , 33, and 61. Lane 1, Molecular weight marker (Hae III digest of FX 174); PCR 14 + IWDO, lanes 2-9: lane 2, HPV6 ; lane 3, HPV 11 ; lane 4, HPV16 ; lane 5, HPV18 ; lane 6, HPV31; lane 7, HPV33; lane 8, HPV61 ; lane 9, human placental DNA suspected of being infected with HPV; PCR 5 + IWDO, lanes 10-17: lane 10, HPV6 ; lone 11 , HPV 11; lane 12, HPV16; lane 13, HPV18 ; lone 14, HPV31 ; lane 15, HPV33 ; lane 16, HPV61 ; lane 17, human placental DNA suspected of being infected with HPV; lane 18, molecular weight marker (Hae III digest of FX174 and HinD III digest of 1 DNA) .

EXAMPLE 4

The following reagents were mixed in a 0.5 mL polypropylene ᴗbe as follows for the Ligase Chain Reaction (LCR):

Reagent	Volume	Final Concentration
Water	21 µL	
Reaction Buffer	10 µL	50 mM EPPS pH7.8
		10 mM NH_4Cl
		10 mM $MgCl_2$
		100 mM K^+ (from all sources)
		0.001% BSA
		1 mM DDT
Nicotine Adenine Dinucleotide (NAD)	0.5 µL	100 µL
ProbeA (sense)	4 µL	5.0 x 10^{11} molecules
ProbeA' (antisense, 5'-phosphate)	4 µL	7.5 x 10^{11} molecules
ProbeB (sense, 5'-phosphate)	4 µL	7.5 x 10^{11} molecules
Probe B' (antisense)	4 µL	5.0 x 10^{11} molecules
Target (including human placental carrier DNA at 10 µg/mL)	1.5 µL	15 ng/50 µL
DNA ligase, <u>Thermus therpophilus</u>	1 µL	

This reaction mixture was overlayed with 30 µL of mineral oil. The tube was placed in an instrument capable of incubation at several temperatures (e.g. thermal cycler from Coy Laboratory Products (Ann Arbor, MI) or the Programmable Cycler Reactor™ (available from Ericomp, San Diego, CA), and then subjected to several cycles of programmed temperature change. Each cycle involved incubation at 50°C for one minute and 85°C for one minute.

EXAMPLE 5

The following procedure was used when performing the Ligase Chain Reaction (LCR), which is described in published European Patent Application No. 0 320 308 A2. The reagents of Example 4 were utilized in the procedure as follows: Two probes (A and B) complementary to immediately adjacent to regions of a target sequence were hybridized and ligated. This ligated probe was denatured away from the target, and hybridized with two additional probes (A' and B') of sense opposite to the initial probes (A and B). The secondary probes then were ligated. Subsequent cycles of denaturation/hybridization/ligation created the formation of double-length probes of both + and - sense.

EXAMPLE 8

The following sequences were determined to be specific for a portion of the E6 region of HPV type 16:

Probe	SEQ ID No.	Sequence	Maps to:
LCR5A	81	GCTGCAAACA ACTATACATG ATATAA	157 - 182
LCR5A'	82	pTTATATCATG TATAGTTGTT TGCAGC	182 - 157
LCR5B	83	pTATTAGAATG TGTGTACTGC AAGCA	183 - 208
LCR5B'	84	TGCTTGCAGT ACACACATTC TAATA	208 - 157

EXAMPLE 9

Base-denatured plasmids which contained full-length papilloma virus inserts in pGEM3 were used as targets. These plasm ids were pG3HPV6(+) (HPV6), pSP 65. 11.5 (HPV11), pSP65.168 (HPV16), p63HPV18H(-)(HPV18), p63:HPV31 (HPV31), pLNK322:HPV33 (HPV33), pBR322:HPV35 (HPV35), pUC19:HPV52 (HPV52), pLNK322: HPV58 (HPV58), pUC9:HPV59 (HPV59) and PBR322:HPV61 (HPV61). All of the oligonucleotides used as probes from Example 8 had chemical labels covalently attched at the ends distal from ligation. These labels were: 5'-fluorescein-LCRSA, 3'-fluorescein-LCRSA', 3'- biotin-LCR5B and 5'-biotin-LCR5B'. Covalent attachment was performed by known methods, i.e., reaction of amine-terminated oligonucleotides with FITC or biotin-NHS-ester essentially following the procedures of Kansal et al., Tet. Letters 29:5537-5540 (1988). The thermal cycler used was obtained from Coy Laboratory Products, Ann Arbor, MI.

Following the LCR procedure of Examples 4 and 5, the mixtures were analyzed using a prototype version of the IM_x® instrument (Abbott Laboratories, Abbott Park, IL), following the protocol for microparticle enzyme immunoassays as follows. A 40µL aliquot of an LCR mixture was diluted 1:1 with distilled water. This diluted mixture was incubated with 50µL antifluorescein-conjugated polystyrene microparticles for five (5) minutes to form a suspension of immune complexes on the microparticles. This suspension then was transferred to an inert glass fiber matrix, to which the microparticles became attached. The matrix was washed with buffer (0.3M Nacl, 10 mM TRIS pH8, 0,1%NaN_3), Any immune complexes attached to the glass matrix was detected by using alkaline phosphatase-labeled conjugate that catalyzed the hydrolysis of 4-methylumbelliferone. The rate at which the 4-methylumbelliferone was generated on the matrix was proportional to the concentration of LCR product formed in the reaction mixture.

Referring to FIG. 4, the graph shows the results obtained from performing LCR on 10^7 molecules of the targets in shown. The rate shown is the rate of generation of 4-methylumbelliferone, and is expresssed as fluorescence counts/ second/second. Background signal is approximately 10 c/s/s, as shown by the amplification of human placental DNA. The only values above background are those for sample containing HPV16, and those values are about 60 times background signal.

EXAMPLE 10

The following sequences were determined to be specific for a portion of the E6 region of HPV type 18:

Probe	SEQ ID No.	Sequence	Maps to:
LCR6A	85	CTTCACTGCA AGACATACAA ATAA	172 - 195
LCR6A'	86	pTTATTTCTAT GTCTTGCAGT GAA	195 - 173
LCR6B	87	pCCTGTGTATA TTGCAAGACA GTAT	196 - 219
LCR6B'	88	TACTGTCTTG CAATATACAC AGG	218 - 196

EXAMPLE 11

Plasmids which contained full-length papilloma virus inserts in pGEM3 were used as targets. The plasmids used were those described in Example 9 . All of the oligonucleotides used as probes obtained from Example 10 had chemical labels covalently attached at the ends distal from ligation. The thermal cycler was obtained from Coy Laboratory Products, Ann Arbor, MI.

Following LCR procedure described in Examples 4 and 5, the mixtures were analyzed as described in Example 9 using the prototype version of the IM_x® instrument (Abbott Laboratories, Abbott Park, IL).

Referring to FIG. 5, the graph dislays the results obtained from performing LCR on 10^7 molecules of the targets. The rate shown is the rate of generation of 4-methylumbelliferone, and is expressed as fluorescence counts/second/

second. Background signal is approximately 15 c/s/s, as shown by the amplification of human placental DNA. The only values above background are those for sample containing HPV 8, and those values are about 40 times background signal.

EXAMPLE 12

The following sequences were determined to be specific for a portion of the E6 region of HPV type 18:

Probe	SEQ ID No.	Sequence	Maps to:
LCR7A	89	TATATTGCAA GACAGTATTG GAAC	200 - 223
LCR7A'	90	pGTTCCAATAC TGTCTTGCAA TTTA	223 - 200
LCR7B	91	pTTACAGAGGT ATTTGAATTT GCATT	224 - 249
LCR7B'	92	AATGCAAATT CAAATACCTC TGTAA	249 - 224

EXAMPLE 13

Plasmids which contained full-length papilloma virus inserts in pGEM3 were used as targets. The plasmids were those of Example 9 All of the oligonucleotides from Example 12 which were used as probes had chemical labels covalently attached at the ends distal from ligation. The thermal cycler was as described in Example 11.

Following the LCR procedure of Examples 4 and 5, the mixtures were analyzed as described in Example 9 using the prototype version of the IMx instrument (Abbott Laboratories, Abbott Park, IL).

Referring to FIG. 6 , the graph shows the results obtained from performing LCR on 10^7 molecules of the targets. The rate shown is the rate of generation of 4-methylumbelliferone, and is expressed as fluorescence counts/second/second. Background signal is approximately 15 c/s/s, as shown by the amplification of human placental DNA. The only values above background are those for sample containing HPV 18, and those values are about 80 times background signal.

EXAMPLE 14

The following sequences were determined to be specific for a portion of the E6 region of HPV type 16.

Probe	SEQ ID No.	Sequence	Maps to:
LCR8A	93	GTATGGAACA ACATTAGAAC AGCA	352 - 375
LCR8A'	94	pTGCTGTTCTA ATGTTGTTCC ATAC	375 - 352
LCR8B	95	pATACAACAAA CCGTTGTGTG ATTT	376 - 399
LCR8B'	96	AAATCACACA ACGGTTTGTT GTAT	399 - 376

EXAMPLE 15

Plasmids which contained full-length papilloma virus inserts in pGEM3 were used as targets. All of the oligonucleotides from Example 14 used as probes had chemical labels covalently attached at the ends distal from ligation. The thermal cycler was as described in Example 11.

Following LCR procedure of Examples 4 and 5, the mixtureswere analyzed as described in Example 9 using the prototype version of the IM_x® instrument (Abbott Laboratories, Abbott Park, IL).

Referring to FIG. 7 , the graph details the results obtained from performing LCR on 10^7 molecules of the targets. The rate shown is the rate of generation of 4-methylumbelliferone, and is expressed as fluorescence counts/second/second. Background signal is approximately 10 c/s/s, as shown by the amplification of human placental DNA. The only values above background are those for sample containing HPV 16, and those values are about 36 times background signal.

EXAMPLE 16

The attached Appendix (example 16) discloses the sequences of the invention aligned to known sequences.

EXAMPLE 16

APPENDIX

HUMAN PAPILLOMA VIRUS

ALIGNMENT of TYPES 6, 11, 16, 18, 31, and 33; with CONSENSUS SEQUENCE .

The appendix lists the sequences of HPV types 6, 11, 16, 18, 31, and 33. It also shows where the sequences of this invention line up with respect to these HPV sequences. In addition, the appendix shows where other sequences, known to the Inventors as of 28 September 1990, and claimed or disclosed by or unknown to others, line up with respect to these sequences.

1. Sequences and Regions Claimed by Us;

PCR = Sequences per examples 1 through 3 (only PCR1, PCR5 PCR14 and PCR15)

LCR = Sequences per examples 4 through 14 only

2. Sequences and Regions Unknown to Others and Not Claimed by Us;

PCR = Sequences designated PCR other than those above JJ

LCR = Sequences designated LCR other than those above

3. *Sequences and Regions Claimed by Others;*
(Italics represents antisense sequences)

AUS = International application number (Australians) PCT/AU88/00047 (WO 88/06634)

WL = International application number (Wayne Lancaster, Wayne State University) PCT/US86/00629 (WO 86/05816)

BE = European Patent Application (Belgians) 89.033834 (X= T or U)

C = International application number (CETUS) PCT/US89/03747 (WO 90/C2821)

O = International application number (Oncor) PCT/US89/O1318 (WO 89/09940)

and

4. Sequences and Regions Disclosed by Others.

S = Sarkar, F.H. and Crissman. J.D. *Biotechniques* **9** 180-184 (1990) *(Italics represents antisense sequences)*

```
 6   1      gTTAATAACAATCTTgGTTTAA AAAAtAGGAGGG    ACCGAAA ACGGTTCAACCGAAAA
11   1      cTTAATAACAATCTTAGTTTAA AAAAgAGGAGGG    ACCGAAA ACGGTTCAACCGAAAA
33   1     gtaaACTATAATgCcaAGTTTTA AAAA AGtAGGGtGTAACCGAAA gCGGTTCAACCGAAAA
16   1      actACAATAAT  tcAtGTATA AAA  ctaAGGGcGTAACCGAAA tCGGTTGAACCGAAAc
31   1   TAATA ATAATAAT  ctTAGTATA AAA AAgtAGGGAGTgACCGAAA  GtGgTGAACCGAAAA
18   1 atTAATACtTttaAcaattgTAGTATAtAAA AA  AGGGAGTaACCGAAAacGgtcgGgACCGAAAA

con    --taatata-ta-aa-tcttag-T-tA-AAAaaag-AGGGagtaACCGAAA-acggtt-aACCGAAAa
                                                            C4-GCCAASTTGGCTTTT
                                                            C5-GCCAGCCCTGGCTTTT
                                                            C36-CGGTTSAACCGAAAA
                                                            C37-CGGTCGGGACCGAAAA
                                                            C38-CGGTTSAACCGAAAM
                                                            C39-CGGTTCAACCGAAAM
    O15-ATTAATACTTTTAACAATTGTAGTATATAAA AA  AGGGAGTAACCGAAAACGGTCGGGACCGAAAA-O15
    O24-     ACTACAATAAT  TCATGTATA AAA  CTAAGGGCGTAACCGAAA TCGGTTGAACCGAAAC-O24
                                                            S1-CGGTCGGGACCGAAAA
                                                            S3-ACCGAAAC

 6  58 CGGTTgTATATAAA CCAGCCCtAAAAtTTAGCAaACGAGGCATTATGGAAAGTgcAaATGCCTCCAC
11  58 CGGTTaTATATAAA CCAGCCCAAAAAaTTAGCAGACGAGGCATTATGGAAAGTaAAGATGCCTCCAC
33  62 CGGTgcaTATAtAAAGCA aACATTTTgcagtaAGgtActGCACgACtATGTTTCAAGACaCtgAGGA
16  58 CGGTTaGTATA AAAGCA gACATTTTaTGcaCcAAaAgAGAACtGCaATGTTTCCacAGGA
31  60 CGGTTgGTATATAAAGCAcataGTaTTtTGtgCaAAccTACAgacGCcATGTTcaAaaATCCtgCAGA
18  66 CGGT  GTATATAAA agatgtGagaaacacaCcAcaaTACtatgGCgcgcTTtgAggATCCaaCAcg

con    CGGTt-gtatatAAagcag--ca-a--at--gcaaaca-agcatt-cgatgttt-aagAtcC--c-ga
       GCC-C4                                                 AUS1-ATGCCTCCAC
       GCC-C5
       CGG-C36                                                C67-AAATCCTGCAGA
       CGG-C37                           C68-CCTACAGACGCCATGTTCA-C68
       CGG-C38                    C71-GCAGTAAGGTACTGCAC-C71
       CGG-C39                                                O10-GGATCCAACACG
    O15-CGGT  GTATATAAA AGATGTGAGAAACACACCACAATACTATGGCGCGCTTTGAGGATCC-O15
    O24-CGGTTAGTATA AAAGCA GACATTTTATGCACCAAAAGAGAACTGCAATGTTTCCACAGGA(-O24)
       CGGTG-S1                                  S2-CCGCGCGAAACTCCTAGGTTGTGC-S2
       CGGTTAGTATA AAAGC-S3
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 6  125 GTCTGCAACgaCcATAGACCAGTTGTGCAAGACGTTTAATCTaTCTaTGCAtACgtTGCAAATTaAtT
11  125 GTCTGCAACAtCtATAGACCAGTTGTGCAAGACGTTTAATCTtTCTtTGCACACtcTGCAAATTCAGT
33  129 aaaACCAcGAACaTTgCAtgAtTTGTGCcAAGCaTTGgAgACAACTATACACAAcATtgAAcTACAGT
16  124 gcGACCcaGAAAgTTaCcacAgTTATGCaCAGagcTGcAAACAACTATACATGAtATAAtATTAgAaT
31  128 aaGACCtcGgAAaTTgCaTGAaCTAaGCtCGGcAtTGgAAAtAcCctacgATGAacTAAgATTgAAtT
18  131 gcGACCctacAAgcTaCcTGAtCTgtGCaCGGaAcTGaAcActtCactgcAaGAcaTAgaAaTaAccT

con     g-gacCaagaa--tTacat-AgtTgtGCa-ggc-tTgaA-a-atCtatgcAt-a-aTa-aAaTaaa-T
        GTCTGCAAC-AUS1          AUS7-GCAAGACGTTTAATCT-AUS7
        AAGACCTC-C67                                      C74-ACACTCTGCAAATTCAGT
    O10-GCGACCCTACAAGCTACCTGATCTGTGCACGGAACTGAACACTTCACTGCAAGACATAGAAATAACCT-O10
    O24-GCGACCCAGAAAGTTACCACAGTTATGCACAGAGCTGCAAACAACTATACATGATATAATATTAGAAT-O24
      S4-CTGGGTCTTTCAATGGTGTCAATA-S4

 6  193 GtGTGTTTTGCAaGAATGCACTGACCACaGCAGAGATtTATtCATATGCaTATAAacACCT[illegible]AGGTc
11  193 GCGTGTTTTGCAgGAATGCACTGACCACcGCAGAGATATATGCATATGCcTATAAgaACCTAAAGGTT
33  197 GCGTGgAaTGCAAaAAACCtTTGCaaCGAtCTGAGGTATATGAtTTTGCaTTTgcaGATTTAAcaGTT
16  192 GTGTGTACTGCAAgcAACAGTTACtgCGAcgTGAGGTATATGAcTTTGCtTTTcggGATTTAtgcATA
31  196 GTGTcTACTGCAAaggtCAGTTAacAgaAACAGAGGTATTaGAtTTTGCATTTAcAGATTTAacaATA
18  199 GTGTaTAtTGCAAgacagtaTTggaActtACAGAGGTATTtGAaTTTGCATTTAaAGATTTAtttgTg

con     GtGTgtatTGCAagaa--catTgacac-a-caGAGgTaTatgaaTtTGCaTtTaaagAttTAa--gT-
                  AUS2-TACGTGACTGGTGGCCGTCTC-AUS2             C73-ACACCTAAAGGTC
        GC-C74                       AUS3-TGAGGTATATGACTTTGCTTTT-AUS3
                                       C60-GAGGTATWTGAHTTTGC-C60    O1-CTAAAGGTT
                                       C61-GAGATWTATKCATATGC-C61    O2-CTAAAGGTT
                  C69-ACAGTATTGGAACTTACAG-C69                       O4-GATTTCCAA
                  C70-CAACAGTTACTGCGACG-C70                         O6-TTATGCATA
                 C72-GACAGTATTGGAACTTACAG-C70                       O7-TTATGCATA
      S5-GTGTTTTGCAGGAATGCACTGACCA-S5                               O8-AATACGTAT
    O10-GTGTATATTGCAAGACAGTATTCGAACTTACAGAGGTATTTGAATTTGCATTTAAAGATTTATTTGTG-O10
                                                                    O11-TTATTTGTG
                                                                    O12-TTATTTGTG
                                                                    O13-AATAAACAC
                                                                    O17-CTAAAGGTC
                                                                    O18-CTAAAGGTC
                                                                    O20-GATTTCCAG
    O24-GTGTGTACTGCAAGCAACAGTTACTGCGACGTGAGGTATATGACTTTGCTTTTCGGGATTTATGCATA-O24
                                                                    O25-TTATTTGTG
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6 261 cTGTttCGAGgCggCTaTCCaTaTGCAGCcTGcGCgTGcTGCcTAGAAtTtCAtGGaAAAATaAACCA
11 261 GTGTggCGAGACaaCTtTCCcTTTGCAGCgTGTGCcTGtTGCTTAGAAcTgCAAGGgAAAATTAACCA
33 265 GTATATAGAGAgGGaAATCCATTTGgAaTATGTaAactgTGTTTgcgGTTcTtATCTAAAATTAGTGA
16 260 GTATATAGAGAtGGgAATCCATATGctGTATGTgAtAAATGTTTAAaGTTTTATTCTAAAATTAGTGA
31 264 GTATATAGgGACGacAcACCACAcGgaGTgTGTacaAAATGTTTAAgaTTTTATTCaAAAgTaAGTGA
18 267 GTgTATAGaGACagtAtACCcCAtGctGcaTGccatAAATGTaTAgatTTTTATTCtAgAaTtAGaGA

con gT-TataGaGacggcaatCCatatGcag-aTGtg--aaaTGttTagaatTttattctAaAaTtAgtgA
C-44*CTCTGYCGWWAGGTAWACGW*-C44 JJ1-aattagnga
C-45*CTCTGTCATATGGCGTACGA*-C45 AUS8-GTGA
C-46*CCCTGCTGTGTGGTGTGCCT*-C46 S6-*GT*
C-47*CYCTGCYGWWWGGTAWACSW*-C47
C-48*CYCTGYYGWWAGGTAWACGW*-C48
C-49*CYCTGYYGWDWGGTAWACSW*-C49
C56-MGAGACRGCWWTCCATWTG-C56
C57-MGAGACRGSWWTCCATWTG-C57
C58-MGAGACRGVWWTCCATWTG-C58
C59-AGAGACAGTATACCGCATG-C59
GTGTGGCGAGACAACTTTCCCTTTGCAGCGTGTGCCTGTTG-O1
GTGTGGCGAGACAACTTTCCC-O2
O3-CAACTTTCCCTTTGCAGCGTGTGCCTGTTG-O3
CACACCGCTCTGTTGAAAGGGAAACGTCGCACACGGACAAC-O4
GTATATAGAGATGGGAATCCA-O6
GTATATAGAGATGGGAATCCATATGCTGTATGTGATAAATG-O7
CATATATCTCTACCCTTAGGTATACGACATACACTATTTAC-O8
O9-*ACCCTTAGGTATACGACATACACTATTTAC*-O9
O10-GTGTATAGAGACAGTATACCCCATGCTGCATGCCATAAATGTATAGATTTTTATTCTAGAATTAGAGA-O10
GTGTATAGAGACAGTATACCG-O11
GTGTATAGAGACAGTATACCCCATGCTGCATGCCATAAATG-O12
CACATATCTCTGTCATATGGGGTACGACGTACGGTATTTAC-O13
O14-*GTCATATGGGGTACGACGTACGGTATTTAC*-O14
O17-CTGTTTCGAGGCGGCTATCCA-O17
O18-CTGTTTCGAGGCGGCTATCCATATGCAGCCTGCGCGTGCTG-O18
O19-*GCCGATAGGTATACGTCGGACGCGCACGAC*-O19
GACAAAGCTCCGCCGATAGGTATACGTCGGACGCGCACGAC-O20
O24-GTATATAGAGATGGGAATCCATATGCTGTATGTGATAAATGTTTAAAGTTTTATTCTAAAATTAGTGA-O24
GTGTATAGAGACAGTATACCG-O25
O26-CAGTATACCCCATGCTGCATGCCATAAATG-O26

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 6  329 ATATAGACACTTTgATTATGCTGgATATGCAaCaACAGTtGAAGAAGAAACtAAacAAGAcATcTTAg
        ||||||||||||| ||||||||| ||||||| | ||||| ||||||||||| ||  |||| || |||
11  329 ATATAGACACTTTAATTATGCTGcATATGCAcCTACAGTAGAAGAAGAAACcAAtgAAGATATtTTAa
        ||||||||| | ||||||| ||| ||||| |  |||| ||||| ||  |   ||  ||  | |
33  333 ATATAGACATTATAATTATtCTGTATATGGAAaTACATTAGAACAAacAgttAAaAAACCTTTaaaTG
         ||||||||||||  ||||  | | |||||||  |||||||||||   |   || ||||| ||   ||
16  328 gTATAGACATTATtGTTATAGTtTGTATGGAACAACATTAGAACAgcaAtacAACAAACCgTTgTGTG
         | ||||   ||| | |||||| |||||||||||||||||||| |       ||||||    | ||||
31  332 ATTTAGAtggTATaGATATAGTGTGTATGGAACAACATTAGAAAAAtTgACaAACAAAGGtaTATGTG
        ||| |||   |||  | |   ||||||||||   ||||| |||||| | || ||||  ||  |||
18  335 ATTaAGAcatTATtcAgActcTGTGTATGGAgacACATTgGAAAAAcTaACtAACActGGgtTATaca

con     aTatAGAcatTaTaattAt-cTgt-TATGgAacaACAtTaGAA-Aa-aaactAAcaaag-t-Tat-tg
        atatagacatt-JJ1
        GTATAGACATTAT-AUS8
                      C50-ATAHSACAYATACSTTGWTGTMATCTT-C50
                      C51-ATAHSACAYATACSTTGWTGTMATC-C51
                      C52-ATAHSACAYATACSTTGWTGTMAT-C52
                    C53-CTGAGACACATACCTCTGTGTGTAACC-C53
                    C54-CTGAGACACATACCTCTGTGTGTAA-C54
                    C55-CTGAGACACATACCTCTGTGTGTA-C55
    O10-ATTAAGACATTATTCAGACTCTGTGTATGGAGACACATTGGAAAAACTAACTAACACTGGGTTATACA-O10
    O24-GTATAGACATTATTGTTATAGTTTGTATGGAACAACATTAGAACAGCAATACAACAAACCGTTGTGTG-O24
        TATATCTGTGAAATTAATACGAC-S6

 6  397 AcGTGcTAATTCGgTGcTACCTGTGTCACAAaCCGcTGTGTGAAgTAGAAAA ggTAAAaCAtATAcT
        | ||| ||||||| || |||||||||||||| ||| |||||||| |||||||   |||| || ||| |
11  397 AAGTGTTAATTCGtTGTTACCTGTGTCACAAgCCGTTGTGTGAAaTAGAAAAA cTAAAgCAcATAtT
        || | |||||| | |||    | ||||| |  || ||||||     |||||||     |        |
33  401 AAaTaTTAATTAGGTGTATTATaTGTCAAAgaCCtTTGTGTCCTcAAGAAAAAaAAcGACATgTGGAT
        |  | ||||||||||||||||  |||||||  ||  |||||||| |||||||  || ||||| ||||
16  396 ATTTGTTAATTAGGTGTATTAacTGTCAAAagCCacTGTGTCCTGAAGAAAAgCAAAGACATcTGGAc
        ||||||||||||||||||| |  |||||||  ||  ||||||| |||||||| ||||||||| ||||
31  400 ATTTGTTAATTAGGTGTATaAcGTGTCAAAgACCGTTGTGTCCAGAAGAAAAACAAAGACATtTGGAT
        |||| ||||| |||||  |   ||| || | |||||||  ||||| ||||||||  |||||  |  ||
18  403 ATTTaTTAATaAGGTGccTgcgGTGcCAgAaACCGTTGaaTCCAGcAGAAAAACttAGACAccTtaAT

con     AttTgtTAATtaGgTGtat--tgTGtCAaAaaCCgtTGtgTccagaAGAAAAaca-agAcatct--at
        AUS4-AATTAATCCACATAAT-AUS4                                AUS9-GATTTATTTG
                                 AUS5-TGTCATAACCTTGAATGTCT-AUS5
    O10-ATTTATTAATAAGGTGCCTGCGGTGCCAGAAACCGTTGAATCCAGCAGAAAAACTTAGACACCTTAAT-O10
    O24-ATTTGTTAATTAGGTGTATTAACTGTCAAAAGCCACTGTGTCCTGAAGAAAAGCAAAGACATCTGGAC-O24
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 6  464 aaccAAGGCgCGgTTCATAAA         gCTAAATtgtacGTGGAAGGG           TCGcTG
            ||||| || ||||||||          ||||||     |||||||||           ||| ||
11  464 gggAAAGGCaCGcTTCATAAAA         CTAAATaaCcaGTGGAAGGG           TCGTTG
           ||        ||||||| |          |      |    || ||||             ||||
33  469 ttAAAcaAAcGATTTCATAATAT         TtcGGGTCGtTGGGCAGGGCGcTGTgcGgCgTGTTG
          |||  || |||| ||||||||            |||||| ||| | || || |||  | | |||||
16  464 AAAAAGcAAaGATTCCATAATATA         aGGGGTCGGTGGACcGGtCGaTGTATGtCtTGTTG
        |||||| || ||||||| || |||          | ||  ||||||| || || || ||  | |||||
31  468 AAAAAGaAACGATTCCACAACATAG         GaGGAaGGTGGACaGGaCGtTGCATagCaTGTTG
         ||||   |||||| ||||||||||            || |   |         |||       |
18  471 gAAAAacgACGATTtCACAACATAGctgggcactataGAgGccaGtgccattcgTGCtgcaaccGagc

con     aaaaAa--acgatTtCAtAA-atag------ctaaaggacg-tgGgcagggcg-tgcatggct-Gttg
        TGGTGTATAGA-AUS9                AUS6-AAATGTATAGATTTTTATTC-AUS6
                                                               C65-CAACCGAGC
    O10-GAAAAACGACGATTTCACAACATAGCTGGGCACTATAGAGGCCAGTGCCATTCGTGCTGCAACCGAGC-O10
    O24-AAAAAGCAAAGATTCCATAATATA         AGGGGTCGGTGGACCGGTCGATGTATGTCTTGTTG-O24

 6  512                     CcTACACTGC         TGGACAACATGCATG    GAAGACaTGT
                            | ||||||||         |||||||||||||||    |||||| |||
11  512                     CtTACACTGC         TGGACAACATGCATG    GAAGACtTGT
                               | |||||         || | ||    ||||    ||
33  528       gaggtcccgACGTAGAGAAACTGCactgtgAcgTGTAAAAacgcCATGagagGACACaagcC
                       ||||||||||||         |  |||||      ||||     ||||    |
16  523 cagatcatcAAGAaCACGTAGAGAAAC       CCAgcTGTAA tCATGCATGGAGAtACAC    C
                 |||| | ||||  |||||       |||  |||||  ||||| |||||| ||||    |
31  527       GagAAGACCtCGTActGAAAC       CCAagTGTAA aCATGCgTGGAGAaACAC    C
              |  | |||  |        |        | |     |    | |  || |   ||      |
18  539 acgacaGgaAcGACtcCaacgacgcAgagaaacaCaAgtataAtattAaGtaTGcAtggACctaaggC

con     --ga--gagaagaccacgta-aga-Actgca---ccaggtgtAaaacatgcaTGgagagAcacaaggc
               C64-GAACACGTAGAGAAAC       CCAG-C64
                 ACGACAGGA-C65
          C66-GAGGTCCCGACGTAGAGAA-C66
    O10-ACGACAGGAACGACTCCAACGACGCAGAGAAACACAAGTATAATATTAAGTATGCATGGACCTAAGGC-O10
    O24-CAGATCATCAAGAACACGTAGAGAAAC       CCAG-O24

 6  547 TACCCTAAAGGA      TATtGTAtTAGACCTGCAaCCTCCaGACCCTGTAGGGTTACATTGCTATG
        ||||||||||||      ||| ||| |||||||||| ||||| |||||||||||||||||||||||||
11  547 TACCCTAAAGGA      TATaGTAcTAGACCTGCAgCCTCCTGACCCTGTAGGGTTACATTGCTATG
         ||  |||||||          ||  ||||         |||||| ||    |   || | |||||||
33  590 aACgTTAAAGGA      ATATGTtTTAGA   TTTatATCCTGAaCCAACTGAcCTATACTGCTATG
         || ||  | ||      |||| | |||||   |||  | || ||  ||||||| || ||||| ||||
16  579 TACaTTGCAtGA      ATATaTGTTAGA   TTTGCAACCaGAGaCAACTGAtCTCTACTGTTATG
        ||| ||||| ||       ||| |||||||   ||||||||| ||| ||||||| ||| |||||||||
31  577 TACgTTGCAAGAC      TATgTGTTAGA   TTTGCAACCtGAGgCAACTGACCTCCACTGTTATG
         || |||||||||      |     |||||        |        |   |||||| |  ||| | |
18  607 aACaTTGCAAGACattgtaTtgcatTTAGAgccccaaaAtgaaattcCggtTGACCTtCtaTGTcAcG

con     tAC-tT--AgGAc-----at-tgt-tTAGAcctt---catcc-ga-cCa--tGaccTacacTG-tAtG
                                          BE16-ACCAGAGACAACXGAXCXCXACXGX-BE16
                              BE18-GXXAGAXXXGCAACCAGAGACAACXGAXCXCXAC-BE18
    O10-AACATTGCAAGACATTGTATTGCATTTAGAGCCCCAAAATGAAATTCCGGTTGACCTTCTATGTCACG-O10
                                                                       C89-G
                                                                       C90-G
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  6 609 AGCAATTAGtAGACAGCTCAGA   AGATGA   GGTGGACgAaGTGGACggACAAGAttCACAACCT
        ||||||||| ||||||||||||   ||||||   ||||||| | ||||||  ||||||  ||||||||
 11 609 AGCAATTAGaAGACAGCTCAGA   AGATGA   GGTGGACaAGGTGGACaaACAAGAcGCACAACCT
        ||||||||   |||||||||||    |||||     |||||  |   ||   ||||   ||||||||
 33 649 AGCAATTAAgTGACAGCTCAGAtGAGGATGAaGgctTGGACcGGCCAGATGGACAA   GCACAACCa
        ||||||||| |||||||||||| ||||| || |   | ||  | |||| |||||||   ||| ||||
 16 638 AGCAATTAAaTGACAGCTCAGAgGAGGAGGATGaaATAGAtgGTCCAGCTGGACAA   GCAGAACCG
        ||||||||   ||||||||||| ||||||||||  |||||  ||||||||||||||   |||||||||
 31 636 AGCAATTAccCGACAGCTCAGAtGAGGAGGATGtcATAGAcaGTCCAGCTGGACAA   GCAGAACCG
        ||||||||  ||||      || || |  ||||  |||||                       | | |
 18 675 AGCAATTAagCGACtcagagGAaGAaaAcGATGaaATAGA  tggagttaatcatcaacatttAcCaG

con     AGCAATTAa--GACagctcaGAtga-gAtGAtga-aT-GAc-gg-c-gatggacaagacgcacAaCcg
        AGCAATTAGWAGAC-C89                BE8-GACGAAGXGGACGGACAAGAXXC-BE8
        AGCAATTAARYGAC-C90       BE9-GA---GGXGGACGAAGTGGACGGACAAGATTCACAACC-BE9
                               BE13-XGA---GGXGGACAAGGXGGACAAAC-BE13
                         BE14-AGAAGAXGA---GGXGGACAAGGXGGACAAACAAGACG-BE14
                                                               BE15-CAGAACCG
                                                          BE17-ACAAGCAGAACCG
                                            C62-CGAAGTGGACGGACAAGAT-C62
                                            C63-CAAGGTGGACAAACAAGACG-C63
    O10-AGCAATTAAGCGACTCAGAGGAAGAAAACGATGAAATAGA  TGGAGTTAATCATCAACATTTACCAG

  6 671 TTAAaACAACATTtCCAAATAgTGACCTGTTG     CTGTGGATGTGAC      AGCAACGTtCGA
        |||| |||||||| ||||||| ||||||||||     |||||||||||||      |||||||| |||
 11 671 TTAACACAACATTACCAAATAcTGACCTGTTG     CTGTGGATGTGAC      AGCAACGTcCGA
           |||    |||||  | || | ||||||||            ||| ||      | ||  || ||
 33 714 GcCACAGCtgATTACtAcATTGTAACCTGTTGT     caCActTGTaAC      ACCACaGTTCGt
        | || |||  ||||| | ||||||||||| ||||      ||   ||| ||      | ||   ||||
 16 703 GACAgAGCCcATTACAATATTGTAACCTTTTGTTG     CAAGTGTgACT      CTACgCTTCGg
        |||| | || ||||||||||  || |||||||||||       ||||| | |      |||| |||||
 31 701 GACAcAtCCaATTACAATATCGTtACCTTTTGTTGT     cAGTGTAAGT      CTACACTTCGt
           |         ||  | | ||| ||    ||||||        |||||||      | | | ||
 18 741 ccCgacgagccgaACcAcAaCGTcACacaaTGTTGTgtatgtgtTGTAAGTgtgaagCcAgAaTTgag

con     g-cacag--cattaCcA-At-gT-ACctgtTGttgt-ctg--g-TGT-Act-----accAcagTtcg-
        GACAGAGCCCAX-BE15                    BE19-AGXGXGACX------CXACGCXXCGG
        GACAGAGCCCA-BE17                BE20-XXGCAAGXGXGACX------CXACGCXXCGG
                                              BE24-XXGXAAGXGXGAAGCCAGAAXXGAG
                                         BE25-AXGXGXXGXAAGXGXGAAGCCAGAAXXGAG
    O10-CCCGACGAGCCGAACCACAACGTCACACAATGTTGTGTATGTGTTGTAAGTGTGAAGCCAGAATTGAG-O10
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 6   728 CTGGTTGTGcAGTGtACAGAaacAGACATCAGAgAAgTgCAAcAgCTTcTGtTGGGaACACTAAAcAT
11   728 CTGGTTGTGgAGTGcACAGAcgGAGACATCAGAcAAcTACAAgAcCTTtTGcTGGGCACACTAAATAT
33   771 TTaTGTGTcaAcACtACAGcaaGtGACcTaCGAACcaTACAgcAaCTacTtATGGGCACAgTgAATAT
16   760 TTGTGcGTACAaAGCACACAcGTAGACATTCGtACtTTGgAAGAcCTGTTAATGGGCACAcTaGGAAT
31   758 TTGTGtGTACAgAGCACACAAGTAGAtATTCGcAtATTGCAAGAGCTGTTAATGGGCtCAtTtGGAAT
18   809 cTagtaGTAgAaAGCtCAgcAGacGAccTTCGagcATTcCAgcAGCTGTTtcTGaaCaCccTgtcctT
con      -Tg--tGTacAgaGcaCAgaag-aGAcaTtcGaacatTgcAa-AgCTgtT-aTGgcaCacTaaa-aT
         XXG-BE19    BE29-AGCAAGXGACCXACGAACCAXACA-BE29    C42-CCCGTGTGAYYYDTA
         XXGXGCGXAC-BE20                                   C43-CTTGTGGGACAGGAA
         CXAGX-BE25
               BE30-AGXACAGCAAGXGACCXACGAACCAXACAGCAACX-BE30
     O10-CTAGTAGTAGAAAGCTCAGCAGACGACCTTCGAGCATTCCAGCAGCTGTTTCTGAACACCCTGTCCTT-O10

 6   796 aGTGTGTCCCATCTGCGC AC    CgAAgaCcTAACAAcGATGGCGGACGATTCAGGTACAGAAAAT
11   796 TGTGTGTCCCATCTGCGC AC    CaAAACCaTAACAAgGATGGCGGACGATTCAGGTACAGAAAAT
33   839 TGTGTGCCCtAcCTGTGC ACAacAAtAAACATCAtCtAcaATGGCcGATcCTGaAGGTACAaAtGgg
16   828 TGTGTGCCCCAtCTGTTCT CAgAAACcATAATCTACcATGGCTGATCCTGCAGGTACcAATGGGGAa
31   826 cGTGTGCCCCAaCTGTTCT aCtAgACtGTAA CTACAATGGCTGATCCAGCAGGTACAGATGGGGA
18   877 tGTGTGtCCgtggTGTgC atCccagCaGTAAgCaACAATGGCTGATCCAGaAGGTACAGAcGGGGA
con      tGTGTG-CCcatcTGtgCtaca-aaacaataatcaaCaAtg---G-t---g--gg---ta-ag-ggat
      C40-CACACRGGGTAGACRCG-C40             C75-ATGGCKGAYCCTGMAGGTAC-C75
      C41-CACACAGGCACCACACG-C41             C76-ATGGCKGAYGATTCAGGTAC-C76
         ACACAC-C42                         C77-ATGGCKGAYCCTTCAGGTAC-C77
         ACACAC-C43                            C81-TACCGMCTRGGACKTCCATG-C81
                                                C82-TACCGMCTRCTAAGTCCATG-C82
                                                C83-TACCGMCTRGGAAGTCCATG-C83
     O10-TGTGTGTCCGTGGTGTGC ATCCCAGCAGTAAGCAACAATGGCTGATC-O10

 6   859 GAGGGGTCtGGGTGTACAGGATGGTTTATGGTAGAAGCtATAGTgcAaCACcCaACAGG      TAC
11   859 GAGGGGTCGGGGTGTACAGGATGGTTTATGGTAGAAGCcATAGTAGAGCACACtACAGG      TAC
33   906 GctGGGAtGGGGTGTACTGGtTGGTTTgAGGTAGAAGCaGTcaTAGAGAgAAgAACAGG      aGA
16   895 GaGGGtACGGGATGTAATGGaTGGTTTTATGTAGAgGCtGTAgTgGAaAaAAAAACAGG      GGA
31   891   GGGgACGGGATGcAATGGtTGGTTTTATGTAGAAGCaGTAaTtGACAgAcAgACAGG      GGA
18   943   GGGcACGGGtTGtAAcGGcTGGTTTTATGTAcAAGCtaTtgTaGACAaAaAaACAGGagatgtaat

con      gagGGgacgGGgTGtA-tGGaTGGTTTta-GTAgAaGCt-TagTagA-aaaaaaACAGG--------a
                C78-TGTAMWGGMTGGTTTTATGT-C78
                C79-TGTAMWGGMTGGTTTGAGGT-C79
                C80-TGTAMWGGMTGGTTTATGGT-C80
                C84-ACATKWCCKACCAAAATACA-C84
                C85-ACATKWCCKACCAAACTCCA-C85
                C86-ACATKWCCKACCAAATACCA-C86
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 6   921 ACAAATATCAGAcGATGAGGAtGAGGAGGTGGAGGACAGTGGGTATGACATGGTGGACTTTATTGATG
11   921 ACAAATATCAGAAGATGAGGAaGAGGAGGTGGAGGACAGTGGGTATGACATGGTGGACTTTATTGATG
33   968 TaATATtTCAGAAGATGAGGAtGAAAcaGcaGATGACAGTGGcacgGATTTacTAGAgTTTATAGATG
16   957 TgcTATaTCAGAtGACGAGAAcGAAAAtGacAGTGATACaGGtGAaGATTTGGTAGAtTTTATAGtaA
31   951 caacATTTCAGAGGACGAAAATGAAgACAGtAGTGATACtGGGGAGGATATGGTtGAcTTTATTGAcA
18  1009 atcagaTgacGAGGACGAAAATG caACAG     AcACaGGGtcGGATATGGTaGAtTTTATTGAtA

con      a-aaat-tcaGA-GA-GAg-AtGaa-a-g-ggatgAcA-tGGgtagGAtaTggTaGAcTTTATtGat-

 6   989 A        CAGcaATATTACA CAcAATTCacTGGAAGCACAGGCATTGTTTAAcAGGCAGGAGGCG
11   989 A        CAGgcATATTACA CAAAATTCtGTGGAAGCACAGGCATTGTTTAATAGGCAGGAGGCG
33  1036 ATtcTAtgGAAaATAgtATACAGGCAGAcACAGAGGCAGCcCgGGCATTGTTTAATAtACAGGAAGgG
16  1025 ATgaTAATGAtTATttaAcACAGGCAGAAACAGAGACAGCACAtGCgTTGTTTAcTGCACAGGAAGCa
31  1019 ATtgTAATGtATAcaacAAtCAGGCAGAAgCAGAGACAGCACAGGCATTGTTTCATGCACAGGAAGCg
18  1071 cacaaggaacATtttgtgAaCAGGCAGAgctAGAGACAGCACAGGCATTGTTcCATGCgCAGGAgGtc

con      attataatgcatatataataCAggcagA--cagaG-cAGCaCagGCaTTGTTtaat-c-CAGGA-Gcg

 6  1048 GAcaCcCATTATGCGACTGTGCAGGACCTAAAACGAAAGTATTTAGGtAGTCCATATGTtAGTCCTAT
11  1048 GAtGCTCATTATGCGACTGTGCAGGACCTAAAACGAAAGTATTTAGGcAGTCCATATGTaAGTCCTAT
33  1104 GAgGATgATTtAaATGCTGTGtgtGcaCTAAAACGAAAGT                     TTGCCgc
16  1093 aAacAACATagAGATGCaGTaCAGGTTCTAAAACGAAAGT              AT TtGGTAGTCCa
31  1087 gAggAACATGCAGAgGCtGTGCAGGTTCTAAAACGAAAGT              ATgTaGGTAGTCCt
18  1139 cAcaAtgATGCAcAaGtgtTGCAtGTTtTAAAACGAAAGT         ttgcaggaggcagcacaga

con      gA-gatcATt-agaggctgTgcagGttcTAAAACGAAAGTatttagg-agtcca--tgtga-tgcc-t
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BE1-XAAAACGAAAGX-BE1

BE2-AGGACCXAAAACGAAAGXAXXXAG-BE2

BE3-AGGXXCXAAAACGAAAGXAXXXGG-BE3

BE4-AXGXXXXAAAACGAAAGXXXGCAG-BE4

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 6 1116 AAaCAcTaTAGCcgAgGCAGTgGAAAGTGAaATAAGTCCACGaTTgGACGCCATTAAACTTACAAgAC
11 1116 AAGCAaTgTAGCTaATGCAGTaGAAAGTGAgATAAGTCCACGgTTaGACGCCATTAAACTTACAAcAC
33 1151 ATGttcacaAagTGcTGCgGagGAcgtTGTtGAtcGTgCTgcaAacCCgtGtAgAAcgtCTATtAaTA
16 1146 cTtAGTGATATTAG      TGGaTGTGTaGAcaATAATATTAGTCCtaGaTTAAAAGCTATATGTA
31 1141 tTAAGTGATATTAG      TaGtTGTGTGGATtATAATATTAGTCCACGGTTAAAAGCTATATGcA
18 1198 aaAcagtccATTAGgggagcggctggagGTGGATacagAgtTaAGTCCACGGTTAcAAGaaATATctt

con     a-aca-tatAttagaggcagtggaa-gtGtggatagt--t-taagtcc--g--taaaagctAta-gta


 6 1184 AGCCAAAAAAGGTAAAGCGACGGCTGTTTcAAACcaGGGAAcTAACGGACAGTGGATATGGCTATTCT
11 1184 AGCCAAAAAAGGTAAAGCGACGGCTGTTTgAAACAcGGGAAtTAACGGACAGTGGATATGGCTATTCT
33 1219 AAaAtAAAgAAtGcAcAtacaGAAAAcGaAAAATAgaTGAgcTAGAAGACAGCGGATATGGCAATACT
16 1207 TAGAAAAAcAAAGTAgAgCtGCAAAAaGgAGAtTATTTGAAagcGAAGACAGCGGGTATGGCAATACT
31 1202 TAGAAAATaAcAGTAAAACaGCAAAAcGaAGACTcTTTGAAcTtcCAGACAGCGGGTATGGCAATACT
18 1266 TAaAtAgTgggcagAAAAagGCAAAAaGgcGgCTgTTTacAaTatCAGAtAGtGGcTATGGCtgTtCT

con     -a-aaAaaaag-g-Aaa--ag-aaaa-g-a-aatatttgaacta-caGAcAG-GGaTATGGC-aT-CT

                                                         JJ3-tatggctattct
                                                         C87-ATACCGTTAWGA
                                                         C88-ATACCGAYAWGA


 6 1252 GAAGTGGAAGCTGgaacgggAACG CAGGTAGAGAAACA                        TGGCG
11 1252 GAAGTGGAAGCTG      cAACG CAGGTAGAGAAACA                        TGGCG
33 1287 GAAGTGGAAACT    CAGCAGAT GGTA     cAACA                        GGTAG
16 1275 GAAGTGGAAACT    CAGCAGAT G        tTACA                        GGTAG
31 1270 GAAGTGGAAAC    gCAGCAGAT G        gTACA                        GGTAG
18 1334 GAAGTGGAAgC    aacaCAGATtcaggtaacTACAaatggcgaacatggcggcaatgtatGTAG

con     GAAGTGGAA-Ctg----gca-caGataggtagag--ACA-------------------------GtaG
        gaagtggaagctgnnnnncnacagat-JJ3
        CTTCACCT-C87
        CTTCACCT-C88
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 6 1295                     taCCGGAAAATGG                  GGGAGATGGTCAGGAAAaGGA
11 1289 A                    cCCGGAAAATGG                  GGGAGATGGTCAGGAAAgGGA
33 1321 A                    AagtcAAAATGG           cgACAC AaActtaaAtGActtaGA
16 1306 A                    A      gggcGccatgagactgAAACACcAtgtagtcAgtAtagtGg
31 1301 A            GGAG        CAAC              AAACA                      AC
18 1396  tggcggcagtacGGAGgctatagaCAACgggggcacagagggcAACA                     AC

con     a------------ggag----aacgcaaaatgg----aga--gaaacacgagatggtcaggaaaggga

 6 1329 CACAGGaAGGGACATAGAGGG       GGaGGAACATAcAGAGGCGGAAGCgcccacaaACAGtgtaC
11 1323 CACAGGgAGGGACATAGAGGGTgagGgGGTGGAACATAgAGAGGCGGAAGCagtagacGACAGcaccC
33 1358 atCtAGTGGGGtgGGgGAtGaTtcaGAaGTaAGctGTgagacaaatGtAGaTagctGTGAAA
16 1349 tggAAGTGGGGgtGGttgcagTcagtAcaGTAGTGGaagtggGGGAGagGgTgtTAGTGAAAGAcAcA
31 1317 AttAAGT               tgtaATgGTAGTG      ACGGGA     cAcATAGTGAAcGAgAgA
18 1445 A             gcagtgtagacggTacaAGTG      AC         aAtAgcaatAtaGAaAat

con     a-caagtagggacagaga-ggt-agga-g--agtgataga-cgg--gaagca---agtgAaaga-a--

 6 1391 GgGAGCATGCAGgCACAgCAGGAATAT  TgGAATTgtTAAAATGTAAaGATtTAC  GggCagCATT
11 1391 GaGAGCATGCAGACACAtCAGGAATAT  TAGAATTacTAAAATGTAAgGATATAC  GAtCtACATT
33 1420         atgttACgttgCAGGAA AT  TAGtAATGTTCTAcAtAgTAGTAATACAAAAGCAAatAT
16 1417 cTatAtgcCaAACACcacttacAA ATATTTTaAATGTaCTAAAAACTAGTAATGCAAAgGCAGCaAT
31 1361 aTgAAaCtCCAACAC       GtA ATATATTgcAaGTGTTAAAAACTAGCAATGgtAAAGCtGCTAT
18 1487 gTaAAtCcaCAAtgtaccataGcAcAatTAaaagActTGTTAAAAgtaAaCAATaaacAAGgaGCTAT

con     gtgaa--t-caa-c-ca-caggaAtAtattagaaatgtt-tAaaaa--ag-aaTacaaaagcagc-aT

 6 1455 ACtTGGTAAGTTTAAAGAaTGCTTTGGCTGTCtTTTaTaGATTTAATTAGGCCATTTAAAAGTGATA
11 1455 ACaTGGTAAGTTTAAAGAcTGCTTTGGCTGTCaTTTgTtGATTTAATTAGGCCATTTAAAAGTGATA
33 1478 ATTAtaTAAATTTAAAGAGgcCTATGGaaTaAGTTTTaTgGAATTAGTAAGACCATTTAAAAGTGATA
16 1484 GTTAGcaAAATTTAAAGAGTTATAcGGgGTgAGTTTTtcaGAATTAGTAAGACCATTTAAAAGTAATA
31 1422 GTTAGgtAAATTTAAAGAaTTATATGGtGTAAGTTTTAtgGAAcTAaTTAGgCCATTTcAAAGcAATA
18 1555 GTTAGcagtATTTAAAGAcacATATGGcTAtcaTTTAcaGAttTAgTTAGaaatTTTaAAAGtgATA

con     -ttaggtaaaTTTAAAGA-t--TatGGcT---tTTTataGA-tTA-TtAG-ccaTTTaAAAGtgATA
                                                JJ4-ttagttagaccatttaaaagtgata
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6  1523 aAACaACATGTttaGATTGGGTGGTaGCAGGgTTTGGTATACATCATAGCATAtCAGAgGCATTTCAA
11 1523 gAACcACATGTgCcGATTGGGTGGTtGCAGGATTTGGTATACATCATAGCATAGCAGAtGCATTTCAA
33 1546 AAACAAgcTGTaCcGATTGGTGTATaaCAGGATaTGGAATTAgTCCatcagTAGCAGAaAGTTTAAAA
16 1552 AAtCAACgTGTtgcGATTGGTGTATtGCTGCATTTGGAcTTACACCcAgtaTAGCtGAcAGTaTAAAA
31 1490 AAAgCACaTGTACtGATTGGTGTgTAGCTGCgTTTGGAGTTACAggtACAgTtGCAGAAGGATTTAAA
18 1623 AAAcCACgTGTACaGATTGGgtTacAGCTataTTTGGAGTaAacccaACAaTaGCAGAAGGATTTAAA

con     aAac-AcaTGTacaGATTGG--t-tagC-ggaTtTGGaaT-aatccta-aaTagCaGAaggatTtaAA
        aaacaacNtgtNcagattgg-JJ4

6  1591 AAaTTAATTGAGCCATTAAGTTTATATGCACATATACAATGGCTaACAAATGCATGGGGAATGGTAtT
11 1591 AAgTTAATTGAGCCATTAAGTTTATATGCACATATACAATGGCTtACAAATGCATGGGGAATGGTAcT
33 1614 gtATTAATTaAACAgcATAGTTTgTATaCtCATtTACAATGTTTAACtTGcGataGaGGAATaaTAaT
16 1620 ACACTATTaCAACAATATTGTTTaTATTtaCAcaTtCAAAGTTTAGCATGTTCaTGGGGAATGGTTgT
31 1558 ACcCTATTgCAACCATATTGTTTgTATTgCCATtTaCAAAGTTTAGCATGTTCcTGGGGcATGGTTAT
18 1691 ACaCTAaTaCAgCCATtTataTTaTATgcCCATaTtCAAtGTcTAGacTGTaaaTGGGGagTatTaAT

con     aca-TAaTtcA-Ccat-tagtTTaTATgcaCAtaTaCAAtGt-Ta-catgtgcatGgGGaaTggTaaT

6  1659 gTTAGTATTAtTAAGaTTTAAAGTAAATAAaAGtAGAaGTACCGTtGCACGTACAcTtGcaACGcTAT
11 1659 ATTAGTATTAATAAGgTTTAAAGTAAATAAgAGCAGATGTACCGTgGCACGTACAtTaGGTACGTTAT
33 1682 ATTAtTgTTAATtAGATTTAggTGTAGcAAAAACAGgTtAACAGTaGCAAAAcTAaTGaGTAAtTTAT
16 1688 GTTAcTaTTAGTaAGATaTAAATGTGGAAAAAATAGAgaAACAATTGAAAAATTgcTGtcTAAAcTAT
31 1626 GTTAaTgCTtGTGAGATtTAAATGTGcAAAAAATAGAaTAACAATTGAAAAATTaTTAgaaAAATTAT
18 1759 aTTAgccCTgtTGcGtTacAAATGTGgtAAgAgTAGAcTAACAgTTGctAAAggtTTAagtAcgTTgT

con     -TTAgtatTa-TaaGaTttAaatgt-gtAAaA-tAGa-taACagTtGcaaaa-tatTaggtA-gtTaT

6  1727 TAAATATACCTGAAAAcCAaATGTTAATaGAGCCaCCaAAAATACAAAGTGGtGTtgcAGCCCTGTAT
11 1727 TAAATATACCTGAAAAtCAcATGTTAATtGAGCCtCCtAAAATACAAAGTGGcGTAcGAGCCCTGTAT
33 1750 TATcaATACCTGAAAcaTGTATGgTtATAGAGCCaCCAAAATTACGgAGccaAaCAtGtGCATTGTAT
16 1756 TATGTgTgTCTcCAAtgTGTATGaTgATAGAGCCtCCAAAATTgCGTAGtACAGCAGCAGCATTATAT
31 1694 TgTGTaTATCTaCAAaTTGTATGTTAATTCAGCCACCcAAATTaCGTAGcACAGCTGCAGCATTATAT
18 1827 TacacgTAcCTgaAAcTTGTATGTTAATTCAaCCACCaAAATTgCGaAGtAgtGtTGCAGCAcTATAT

con     TatataTacCTgaAAattgtATGtTaAT-gAgCCaCCaAAAtTaCgaAGtagag--gcaGCa-T-TAT
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 6 1795 TGGTTTcGtACAGGtATaTCAAATGCcAGTACAGTTATAGGGGAaGCaCCaGAATGGATAACaCGCCA
11 1795 TGGTTTAGgACAGGcATtTCAAATGCaAGTACAGTTATAGGGGAgGCgCCgGAATGGATAACgCGCCA
33 1818 TGGTTTAGAACAGCaATgTCAAAcATTAGTGAtGTacAAGGtacaACaCCtGAATGGATAgAtAGACt
16 1824 TGGTATAaAACAGGtATaTCAAAtATTAGTGAaGTgTATGGaGAcACgCCAGAATGGATAcAAAGACA
31 1762 TGGTAcAGAACAGGAATgTCAAAcATTAGcGAtGTATATGGtGAaACACCAGAATGGATAgAAAGACA
18 1895 TGGTAtAGAACAGGAATaTCAAAtATTAGtGAaGTAatgGGaGAcACACCtGAgTGGATAcAAAGACt

con     TGGT-tagaACAGgaATaTCAAAtattAGtgaaGTaa-aGG-gaaaCaCCaGAaTGGATA-aaaGaCa
                 BE32-AXAXCAAAXAXXAGXGAAGX-BE32   JJ6-tggataNaaagaca

 6 1863 aACaGTTATTGAACAcgGgTTGGCaGACAGTCAgTTTAAATTAACaGAAATGGTGCAGTGGGCgTATG
11 1863 gACcGTTATTGAACATAGtTTGGCTGACAGTCAATTTAAATTAACTGAAATGGTGCAGTGGGCATATG
33 1886 AACtGTTTTACAACATAGcTTTAATGATAaTAtATTTGAtTTAAgTGAAATGGTACAGTGGGCATATG
16 1892 AACAGTATTACAACATAGTTTTAATGATtgTACATTTGAaTTATCaCAgATGGTACAATGGGCcTAcG
31 1830 AACAGTATTACAgCATAGTTTTAATGAcAcaACATTTGATTTGTCcCAAATGGTACAATGGGCATATG
18 1963 tACtaTtaTACAaCATgGaaTagATGAtAgcAatTTTGATTTGTCagAAATGGTACAATGGGCATtTG
con     aACagTt-TacAaCAtaGttTt-atGA-agtaaaTTTgA-TTa-cagAaATGGTaCA-TGGGCaTatG
        aacNgttatacaacatagtttNgatgat-JJ6

 6 1931 ATAATGAcATaTGcGAgGAgAGTGAaATtGCATTTGAATATGCACAaaGgGGAGAtTTTGAtTCtAAT
11 1931 ATAATGAtATtTGtGAaGAaAGTGAgATaGCATTTGAATATGCACAgCGTGGAGAcTTTGAcTCcAAT
33 1954 ATAAcGAgtTAacgGACGATAGTGAcATTGCATATtAtTATGCACAACTTGCAGAtTCaAATAGTAAT
16 1960 ATAATGAcaTAgTaGACGATAGTGAAATTGCATATAAATATGCACAATTgGCAGACACTAATAGTAAT
31 1898 AcAATGAtgTtATgGATGATAGTGAAATTGCcTATAAATATGCACAATTAGCtGACAGTgATAGTAAT
18 2031 AtAATGAgcTgAcaGATGAaAGcGAtATgGCaTtTgAATATGCcttATTAGCaGACAGcaAcAGcAAT

con     AtAAtGA-aTaa--GA-GAtAGtGAaATtGCaT-TgAaTATGCacaatt-GcaGAc--t-AtagtAAT

 6 1999 GCAcGaGCaTTTTTAAATAGcAATATGCAGGCaAAATATGTgAAAGATTGTGCAAcTATGTGtAGACA
11 1999 GCAaGgGCcTTTTTAAATAGTAATATGCAGGCtAAATATGTAAAAGATTGTGCAATTATGTGcAGACA
33 2022 GCtgcTGCaTTTTTAAAAAGTAAcTCACAaGCAAAAATaGTAAAGGAcTGTGgAATAATGTGTAGACA
16 2028 GCAaGTGCcTTTcTAAAAAGTAATTCACAGGCAAAAATtGTAAAGGATTGTGcAACAATGTGTAGACA
31 1966 GCAtGTGCaTTTTTAAAAAGTAATTCgCAGGCAAAAATaGTtAAAGATTGTGgAACAATGTGTAGACA
18 2099 GCAgcTGCcTTTTTAAAAAGcAATTgcCAaGCtAAAtattTaAAAGATTGTGccACAATGTGcAaACA

con     GCa-gtGC-TTTtTAAAaAGtAAttcgCAgGCaAAA--tgTaAAaGAtTGTGcaAcaATGTGtAgACA
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 6 2067 TTATAAACATGCAGAAATGAggAAGATGTCTATaAAACAATGGATaAAacATAGGGGTtCTAAAaTaG
11 2067 TTATAAACATGCAGAAATGAaaAAGATGTCTATtAAACAATGGATtAAgtATAGGGGTaCTAAAgTtG
33 2090 TTATAAAaAAGCACAAAAAcgtAAAATGTCaATagGACAATGGATAcAAagTAGATGTGAaAAAacAa
16 2096 TTATAAACGAGCAGAAAAAaaACAAATGagtATGaGtCAATGGATAAAAtaTAGATGTGAtAggGTAg
31 2034 TTATAAACGAGCAGAAAAACGACAAATGtccATGgGACAGTGGATtAAAagTAGATGTGAcAAAGTta
18 2167 TTATAggCGAGCccAAAAACGACAAATGaatATGtcACAGTGGATacgAttTAGATGTtcaAAAaTag

con     TTATAaac-aGCagAAAaa-ga-AaATGtctATgagaCAaTGGATaaaataTAGatGTg-tAaa-tag
                                         JJ11-tggataaaatatagatgtNctaaaatag

 6 2135 AagGcacAGGaAAtTGGAAaCCAATTGTaCAaTTcCTAcGACATCAAAAtATAGAATTcATTCCtTTT
11 2135 AcaGTGtAGGtAAcTGGAAgCCAATTGTgCAGTTtCTAaGACATCAAAACATAGAATTTATTCCATTT
33 2158 ATGATGGAGGaAATTGGAgaCCAATaGTaCAGTTgTTAAGATATCAAAACATtGAATTTAcagCATTT
16 2164 ATGATGGAGGTGATTGGAaGCAAATtGTtAtGTTTTTAAGgTATCAAggtgTAGAgTTTATGTCATTT
31 2102 gTGAcGaAGGTGAcTGGAGGgAcATAGTaAAGTTTTTAAGATATCAACAAATAGAaTTTgTGTCATTT
18 2235 aTGAaGggGGaGAtTGGAGaccaATAGTgcAaTTccTgcGATAcCAACAAATAGAgTTTaTaaCATTT
con     atgatggaGG--AtTGGA--ccaAT-GTacagTTt-TaaGatAtCAAaa-aTaGAaTTtat--CaTTT
        atgatggaggaaattgga-JJ11                                   JJ12-cattt

 6 2203 TTAActAAAtTtAAATTATGGCTGCACGGtACGCCaAAAAAAAAcTGcATAGCCATaGTAGGcCCtCC
11 2203 TTAAGcAAAcTaAAATTATGGCTGCACGGaACGCCcAAAAAAAAtTGTATAGCCATTGTAGGgCCACC
33 2226 TTAgGTGCATTtAAAAagTTTTTaaAAGGtATACCaAAAAAAAgcTGTATgcTAATTTgTGGaCCAGC
16 2232 TTAaCTGCATTAAAAAgaTTTTTgcAAGGcATACCtAAAAAAAAtTGcATaTTAcTATATGGTGCAGC
31 2170 TTAtCTGCATTAAAgctgTTTTTAAAAGGAgTgCCaAAgAAAAAcTGTATtTTAaTAcATGGTGCAcC
18 2303 TTAggaGCcTTAAAatcaTTTTTAAAAGGAaccCCcAAaAAAAAtTGTtTagTAtTttgTGGacCAgC

con     TTAa-tgcatTaAAattaTtttT--AaGGaa-gCCaAAaAAAAa-TGtaTagtaaT-t-tGG-cCa-C
        ttaagtgcattaaaattatttttgcaaggNacNccNaaaaaaaa-JJ12

 6 2271 aGAtACTGGGAAaTCGTaCTTTTGtATGAG TTTAATaAgcTTTcTaGGaGGtACAGTTATTAGTcAT
11 2271 tGAcACTGGGAAGTCGTgCTTTTGcATGAG TTTAATtAAGTTTTTgGGgGGaACAGTTATTAGTTAT
33 2294 aAAtACAGGaAAGTCATatTTTGGaATGAG TTTAATacAGTTTTTaaAAGGGTgTGTTATATcaTgT
16 2300 TAAcACAGGTAAATCATtaTTTGGtATGAG TTTAATGAAaTTTcTgCAAGGGTcTGTAATATgtTtT
31 2238 TAATACAGGTAAATCATATTTTGGAATGAGccTTATTGAgCTTTtTACAAGGATgTaTAATATCATaT
18 2371 aAATACAGGaAAATCATATTTTGGAATGAGttTTAT acaCTTTaTACAAGGAgcagTAATATCATtT

con     -aAtACaGG-AAaTCaTatTTTgGaATGAG-tTTAataaacTTTtTacaaGGatc-gT-ATat--taT
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 6 2338 GTaAATTCCaGCAGCCATTTtTGGtTgCAaCCgtTAgtaGATGCtAAgGTaGCATTgTTaGATGATGC
11 2338 GTtAATTCCtGCAGCCATTTcTGGcTaCAGCCAcTAaCgGATGCAAAAGTgGCATTaTTgGATGATGC
33 2361 GTAAATTCTAAAAGtCAcTTTTGGTTgCAGCCATTAtCAGATGCAAAAATAGGAATGaTAGATGATGt
16 2367 GTAAATTCTAAAAGcCATTTTTGGTTACAACCATTAGCAGATGCcAAAATAGGtATGTTAGATGATGC
31 2306 GcAAATTCaAAAAGTCATTTTTGGTTACAACCAcTgGCtGATGCTAAAATAGGCATGTTAGATGATGC
18 2438 GtgAATTCcActAGTCATTTTTGGTTggAACCgtTaaCaGATaCTAAggTgGcCATGTTAGATGATGC

con     GtaAATTCcaaaAG-CAtTTtTGGtT-cAaCCatTagcaGATgCtAAa-TaG-aaTgtTaGATGATGc

 6 2406 aACACAgCCATGTTGGAtATATATGGATACATATATGAGAAAttTgTTAGATGGTAATCCTATGAGtA
11 2406 cACACAACCATGTTGGACATATATGGATACATATATGAGAAAccTaTTAGATGGTAATCCTATGAGcA
33 2429 aACgCcAatAaGTTGGACATATATAGATGAtTAcATGAGAAATGCgTTAGATGGAAATgaAATTTCaA
16 2435 TACAgtGCCcTGTTGGAAcTAcATAGATGAcaAttTAAGAAATGCATTgGATGGAAATttAGTTTCTA
31 2374 TACAACGCCaTGTTGGcAtTAtATAGAcAAtTAccTAcGAAATGCAcTAGATGGCAAcCCtGTATCTA
18 2506 aACgACcaCgTGTTGGacaTActTtGAtAccTAtaTgaGAAATGCgtTAGATGGCAAtCCaaTAagTA

con     aACaccgccatGTTGGacaTAtaTaGAta--tAtaTgaGAAAtgc-tTaGATGG-AAtcc-aT---tA
              JJ15-gttggacatatatNgatacNtatatgagaaatgcgttagatgg-JJ15

 6 2474 TtGAcAGAAAgCATAaAGCATTgACATTAATTAAaTGTCCACCtCTgCTaGTaACgTCcAAcATAGAt
11 2474 TAGATAGAAAACATAGAGCATTAACATTAATTAAgTGTCCACCgCTaCTgGTTACaTCAAATATAGAc
33 2497 TAGATGTgAAACATAGgGCATTAGTgCAAtTAAAATGTCCACCACTgCTTcTTACcTCAAATAcAAAT
16 2503 TgGATGTAAAGCATAGAcCATTgGTaCAAcTAAAATGcCCTCCATTATTaATTACATCTAAcATtAAT
31 2442 TaGATGTAAAGCATAAAgCtTTAATgCAgtTAAAATGTCCTCCtTTATTgATTACATCTAATATAAAT
18 2574 TtGATagAAAGCAcAAAcCaTTAATaCAacTAAAATGTCCTCCaaTAcTacTaACcaCaAATATAcAT

con     TaGAt--aAAgCAtA-agCaTTaatacaa-TaAAaTGtCC-CCacTacTa-TtACatCaAAtAtaaAt
 6 2542 ATTActAAAGAaGAtAAATAtAAgTATTTACATAcTAGAGTaACaACATTTACATTTCCAAATCCATT
11 2542 ATTAGCAAAGAgGAgAAATAcAAATATTTACATAGTAGAGTtACcACATTTACATTTCCAAATCCATT
33 2565 GCaGGCACAGAcTCTAGATGGCCATATTTACATAGTAGATTaACaGTATTTgaATTTaaAAATCCATT
16 2571 GCtGGTACAGATTCTAGgTGGCCtTATTTACATAaTAGATTGGTGGTgTTTACATTTCCtAATgagTT
31 2510 GCAGGTAAGGATgAcAGATGGCCATAccTACATAGcAGAcTGGTGGTtTTTACATTTCCAAATcCATT
18 2642 cCAGcaAAGGATaAtAGATGGCCATAttTAgAaAGtAGAaTaacaGTaTTTgaATTTCCAAATgCATT

con     gc-ggtAaaGAtgatAgaTggccaTAttTAcAtAgtAGA-TaacagtaTTTacATTTccaAATccaTT
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 6 2610 CCCtTTTGACAGAAATGGGAATGCAGTgTATGAACTgTCAaATaCAAACTGGAAATGTTTtTTTGAAA
11 2610 CCCcTTTGACAGAAATGGGAATGCAGTaTATGAACTATCAGATGCAAACTGGAAATGTTTcTTTGAAA
33 2633 CCCATTTGAtGAAAATGGtAAcCCAGTGTATGcAaTAAATGATGAAAAtTGGAAATCCTTTTTCTCAA
16 2639 TCCATTTGACGAAAACGGAAATCCAGTGTATGAgcTtAATGATAAgAACTGGAAATCCTTTTTCTCAA
31 2578 TCCATTTGACAAAAACGGAAATCCAGTATATGAAtTAAgTGATAAAAACTGGAAATCCTTTTTCTCAA
18 2710 TCCATTTGAtAAAAAtGGcAATCCAGTATATGAAaTAAaTGAcAAAAAtTGGAAATgtTTTTTtgaAA

con     -CCaTTTGAcaaAAAtGG-AAtcCAGT-TATGaacTaaatgAtaaaAAcTGGAAAT--TTtTT---AA

 6 2678 GACTGTCGTCaAGCCTAGACATTcAGGATTCtGAGGA   CGAGGAA   GATGGAAGCAATAGCCAA
11 2678 GACTGTCGTCCAGCCTAGACATTgAGGATTCAGAGGA   CGAGGAA   GATGGAAGCAATAGCCAA
33 2701 GGACGTGGTgCAaATTAGATTTa taGAGGAAGAGGA   CAAGGAAAACcATGGAGGaAATATCagc
16 2707 GGACGTGGTcCAGATTAAgTTTGCACGAGGAcGAGGA   CAAGGAAAACGATGGAGACTCTTTgcCA
31 2646 GGACGTGGTgCAGATTAAATTTGCACGAGGAAGAGGA   CAAAGAAAACGATGGAGACTCTTTCtCA
18 2778 GGACaTGGTcCAGATTAgATTTGCACGAGGAAGAGGAagatgcAGAcAcCGAaGGAaACcCTTTCggA

con     GgacgTgGTccAgatTAgattTgcacGAggaaGAGGA---c-agGAaaacgAtGGA--ca-T-tcc-a

 6 2740 GCGTTTAGATGCGTGCCAGGAaCAGTTGTTAGAACTTTATGAAGAAAACAGTAcTGAcCTACACAAAC
11 2740 GCGTTTAGATGCGTGCCAGGAtCAGTTGTTAGAACTTTATGAAGAAAACAGTAtTGATaTACACAAAC
33 2766 ACGTTTAAATGCagtgCAGGAgAAAATACTAGAtCTTTAcGAAGcTGATAaaACTGATtTACcatcAC
16 2772 ACGTTTAAATGTGTGTCAGGACAAAATACTAacACATTATGAAAATGATAGTACAGAcCTACGTGAcC
31 2711 ACGTTTAAATGTGTGTCAGGACAAAATAtTAGAACATTATGAAAATGATAGTAAAcgaCTttGTGAtC
18 2846 ACGTTTAAgTtgcgtgCAGGACAAAATcaTAGAcCAcTATGAAAATGAcAGTAAAgacaTagacagcC

con     aCGTTTAaaTgcgtg-CAGGAcaAaaTatTAgaaC-tTAtGAA-atgA-AgtAc-gaccTacacaaaC

 6 2808 AtgTatTGCATTGGAAATGCATgaGAcatGAAAGTGTATTAtTAtAtAAAGCAAAACAAATGGGCCTa
11 2808 AcATTaTGCATTGGAAATGCATACGAtTGGAAAGTGTATTAcTAcAcAAAGCAAAACAAATGGGCCTg
33 2834 AaATTGAaCATTGGAAACtgATACGCaTGGAgTGTGCTTTATTgTAtAcAGCCAAACAAATGGGATTT
16 2840 ATATAGACTATTGGAAACAcATgCGCCTaGAATGTGCTaTtTatTAcAAgGCCAGAGAAATGGGATTT
31 2779 ATATAGACTATTGGAAACAtATtCGaCTtGAATGTGtAtTAaTgTATAAAGCAAGAGAAATGGGAATA
18 2914 AaATAcAgTATTGGcAACtaATaCGttggGAAaaTGcAaTAtTcTtTgcAGCAAGgGAAcatGGcATA

con     AtaTagag-ATTGGaAAc-cATacGactgGAa-gTG-atTatt-tataaaGCaA-a-AAatgGG--Ta
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 6 2876 AGCCACATaGGaaTgCAAGTAGTgCCACCATTAAagGTGTCcGAagCaAAAGGACATAATGCcATTGA
11 2876 AGCCACATcGGgtTaCAAGTAGTaCCACCATTAActGTGTCAGAGACtAAAGGACATAATGCtATTGA
33 2902 tcACATtTatGCCACCAgGTGGTGCCttCtTTGttaGcATCAAAGACcAAAGCATTTCAAGtAATTGA
16 2908 aAACATATTAACCACCAaGTGGTGCCAaCacTGgCtGTATCAAAGAatAAAGCATTACAAGCAATTGA
31 2847 CAcAgTATTAACCACCAGGTGGTGCCAGCgTTGtCaGTATCAAAGgccAAAGCcTTACAAGCTATTGA
18 2982 CAgAcatTaAACCACCAGGTGGTGCCAGCcTataacaTtTCAAAaagtAAAGCacataAAGCTATTGA

con     aaccataTaa-ccacCA-GTgGTgCCa-Cattgac-gtaTCaaAgactAAAGca--t-AaGctATTGA
                                          JJ18-tcaaagactaaagcacataaagcNattga

 6 2944 AATGCAAATGCATTTAGAATCaTTAttAAggACTgAGTATaGTaTGGAACCgTGGACATTACAaGAaA
11 2944 AATGCAAATGCATTTAGAATCcTTAgcAAAAACTCAGTATgGTgTGGAACCtTGGACATTACAgGAcA
33 2970 ACTaCAAATGgCaTTAGAgACATTAagTAAATCACAGTATAGTAcaagcCAaTGGACATTgCAAcAaA
16 2976 ACTgCAAcTaACGTTAGAAACAaTAtATAACTCACAATATAGTAATGAaaAgTGGACATTaCAAgAcg
31 2915 ACTaCAAATGAtGTTgGAAACAtTAaATAACACTgAATACAAAAATGAGGAcTGGACAaTGCAgcAaA
18 3050 ACTgCAAATGgcccTacAAggccTtgcacAaAgTcgATACAAAAccGAGGAtTGGACAcTGCAagAcA

con     AcTgCAAaTg-c-tTagAaacatTa---aaaactca-TAtagta--gaaca-TGGACAtT-CAagA-a
        actgcaaatgg-JJ18

 6 3012 CaAGTTATGAAATGTGGCaAACACCACC tAAACGcTGtTTTAAAAAACgGGGcAAaACTGTaGAaGT
11 3012 CcAGTTATGAAATGTGGCTAACACCACC CAAACGgTgCTTTAAAAAACAGGGAAAtACTGTgGAgGT
33 3038 CaAGCTTaGAgGTGTGGCTttgTGaACCACC AaaATGTTTTAAAAAACAaGGAgAaACAGTaactGT
16 3044 ttAGCCTTGAAGTGTATTTAACTGCACCAAC AGGATGTaTAAAAAAACATGGATATACAGTgGAaGT
31 2983 CAAGtCTTGAACTGTATTTAACTGCACCTAC AGGgTGTTTAAAAAAACATGGATATACtGTAGAgGT
18 3118 CAtGcgagGAACTaTggaatACaGaACCTACtcactgcTTTAAAAAA ggTGGccAaACaGTAcAaGT

con     caaG-t-tGAa-TgTggctaac-gcACCaacaa-g-tgttT-AAAAAacatGGa-A-AC-GTagaaGT

 6 3079 tAAATTTGA   TGGCTGTGcAaACAATacAATGGAtTATGTGGTATGGACAgATgTgTATgTGCAGG
11 3079 aAAATTTGA   TGGCTGTGAAgACAATgtAATGGAgTATGTGGTATGGACAcATATATAccTGCAGG
33 3105 GCAATaTGA   caatGACAAAaAaAATACAATGGATTATACAAACTGGgtgAaATATATATTataG
16 3111 GCAgTTTGATGG   aGACATATgCAATACAATGCATTATACAAACTGGAcAcATATATATATTTGTG
31 3050 GCAaTTTGATGG   tGAtGTAcACAAcACcATGCATTATACtAACTGGAaAtTTATATAccTaTGTa
18 3185 atAtTTTGATGGcaacaAaGacaAttgtAtgAcctATgtagCatgggacAgtgTgtatTAtaTgacTg

con     gcAaTtTGAtggcaacgatgaaaacaatacaAtggAttat-caaactggacagatataTAtaTg--tg
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 6 3144 ACAAtGACaCcTGGGTAAAgGTgcaTAGTatgGTAGATGCtAAGGGtATATATTAcACATGTGGACAA
11 3144 ACAAcGACtCATGGGTAAAaGTaACTAGTtccGTAGATGCcAAGGGcATATATTATACATGTGGACAA
33 3170 AgGAAGAtaCATGtACTATGGTtACaGGgaAAGTAGATTATAtaGGTATgTATTATATACATaActGt
16 3176 AAGAAGcatCAgtaACTGTGGTaGAgGGtCAAGTTGAcTATtAtGGTtTaTATTATGTtCATGAAGGA
31 3115 tAGAtGGccaATGtACTGTtGTgGAaGGgCAAGTTAATTgTAAGGGcaTtTATTATGTACATGAAGGA
18 3253 atGcaGGaacATGggacaaaaccGctacctgtGTaAgTcacAgGGGatTgTATTATGTAaAgGAAGGg

con     a-gaaGacacatgg-cta-ggt-g-t-gt-aaGTagattataagGGtaTaTATTAt-tacatgaagga

 6 3212 TTTAAAACATATTATGTAAAcTTTgtaAAAGAGGCAgAAAAGTATGGgAGcACCAAaCATTGGGAAGT
11 3212 TTTAAAACATATTATGTAAATTTTAAtAAAGAGGCAcAAAAGTATGGTAGtACCAAtCATTGGGAAGT
33 3238 gaAAAggtATATTTTaaAtATTTTAAAGAgGATGCtGcAAAGTATtcTAAAACacAAaTgTGGGAAGT
16 3244 atAcgAACATATTTTGTgcAgTTTAAAGAtGATGCAGAAAAATATaGTAAAAaTAAAgTATGGGAAGT
31 3183 cAtAtAACATATTTTGTAaAtTTTAcAGAaGAgGCAaAAAAATATGGGActggTAAAAaATGGGAAGT
18 3321 tAcAacACgTtTTaTaTAgAaTTTAaAagtGAatgtgAAAAATATGGGAacacaggtAcgTGGGAAGT

con     t-taaaacaTaTT-TgtaaAtTTTaaa-aaGAggcagaAAA-TATgg-Aa-ac-aaaaa-TGGGAAGT

 6 3280 ATGTTATGGCAGCACAGTTAT   ATGTTCTCCTGC   ATCTGTATCTAGCACTacACaAGAAGTAT
11 3280 ATGTTATGGCAGCACAGTTAT   ATGTTCTCCTGC   ATCTGTATCTAGCACTgtACgAGAAGTAT
33 3306 ACATGtGGGTGGTCAGGTAAT   tgTTTGTCCTAC   gTCTaTATCTAGCA   ACCA   AaTAT
16 3312 tCATGCGGGTGGTCAGGTAAT   atTaTGTCCTACATCTGTgTTTAGCAGCA   ACGA   AgTAT
31 3251 gCATGCGGGTGGTCAGGTAATTG   TTTtTCCTgaATCTGTaTTTAGCAG   TGACGA   AaTAT
18 3389 aCATtttGGgaaTaAtGTAATTGattgTaaTgactctatgtgcagTAcCAG   TGACGAcacggTAT

con     acaT---GGt-gt-agGTaATtg-at-tt-Tcctgcatc-tct-t--c-AGcactgac-aagaagTAT
                                                                 BE21-CGGTAT

 6 3342 CCATTcCTGAA tCTACTACATACACCCCCGCACAGACC tCcaCCCT  tGTGTCCtCaaGC   AC
11 3342 CCATTgCTGAA CCTACTACATACACCCCCGCACAGACCacCgcCCCTacaGTGTCCgCctGC   AC
33 3362 CCACTaCTGAAACTgcTgACATACA     gACAGAC     AAC   gaTaacCGACC   AC
16 3371 CCTCTcCTGAAAtTATTaggcagCA     cttgGCC     AACcACcCCgCCgCGACCcATAC
31 3310 CCT   tTGCTggGATTGTTAcAaAGCTACcaacaGCC    AACaACACCaCCaCAtCGaATTC
18 3454 CC   gcTaCTcaGcTTGTTAaAcAGCTAC             AgcACACCcCCtCAcCGtATTC

con     CCact-cTgaaa---ttgacatacAcccacgcacagacc--c--caacaac-cctcc-Caacc-ataC
        CC---GCXACXCAGCXXG-BE21
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 6 3403 CA                                  aGGAAGACGcaGTGcaaaCGCCGCCTAGGAAaCG
11 3406 CAC                                  GGAAGACGGcGTGtcggCGCCGCCTAGGAAgCG
33 3410 CACAAGC                       agcggccAAACgacGACGAC    cTgCAGacACCA
16 3426 CA AAGCCgtCGCCTTGGGCACC    GAAG        AAACacaGACGAC    TATcCAGCGACCAAGA
31 3368 CA AAACCtgCGCCTTGGGCACCaGtGAAGgtgTgCGGCgggcGACGACGTCTActaAGCGACCAAGA
18 3503 CA gcACCgtgtCCgTGGGCACC GcaAAGaccTaCGGC      caGACGTC
                                             BE10-GGCGXGXCGGCGCCGCCXAG-BE10

con     CAcaaaccgtcgccttgggcacc-g-gaaggcgtacgaagac-gacgacgtcc-cc-ag--accaaca

 6 3439 AGCACGaggagtccaACaGTCCcCTtgCAACgCCtTGTGTGTGGCCcACATtgGAcCCGTGGACAGTg
11 3442 AGCACG      tggACCGTCCaCTaaCAACaCCcTGTGTGTGGCCaACATCaGAtCCGTGGACAGTA
33 3449        CAGACACCGCCcAgCCCCT   tacaaAgcTGTTctGTGCA gaCccCgCCtTGGACAaTA
16 3481 tCAGAGCCAGACACCG GAAACCCCTgCCACaCCActAAGTTGTTGCAcaGaGACTCaGTGGACAGTG
31 3435 aCAGAGCCAGAGcaC aGAAACaCCCaCCACcCCAacAAGTTGTTGCGAgGCGACTCcGTGGACAGTG
18 3548           GgctgctAcACgaCCtggACaCtgtggAcTcGcgGaGAaGCagCattGTGGAC cTG

con     acaaagccaga--ccgc-aaaCccct-c-acaccatgt-tttggtgcacagcggctccgTGGACagTg

 6 3507 gAAaCcACAACcTCaTCACTaAC    AATcACgACcAGCACCAAA     GAcGG    AACAACaG
11 3504 cAAtCaACAACATCGTCACTgAC    AATtACAACAAGCACCAAA     GAaGG    AACAACTG
33 3506 gAACAgcaCgtACTGCAACTAACtGC    aCAAACAAGCAgCGGA     cTgtGTGT    AgTTc
16 3548 cTCCAaTcCtcACTGCAttTAACAGCT    CACACAAAggACGGA     tTaaCTGT    AaTag
31 3502  TCAACTgtggggTTaTCaGTGCAGCT gcatgCACAAAccAAACAA     GGgCTGTCaGTtGTcc
18 3604  TCAAC   ccacTTcTCgGTGCAGCTacacctacaggcaacAACAAagacGGaaacTCtGTaGTgg

con     c--aac-c--cactgc-actaaCagctaat-c-aacaagcacca-Aa------gggtgtcaaca-t-g

 6 3562 TaACAGTtCAGCTACGCCTATAGTGCAAtTtCAAGGTGAaTCCAATTGTTTAAAgTGTTTTAGATATA
11 3559 TcACAGTGCAGCTACGCCTATAGTGCAAcTgCAAGGTGAtTCCAATTGTTTAAAATGTTTTAGATATA
33 3561 TAACgtTGCA        CCTATAGTGCATTTAAAAGGTGAaTCaAATAGTTTAAAATGTTTAAGATA
16 3603 TAACACTACA        CCcATAGTACATTTAAAAGGTGATGCtAATAcTTTAAAATGTTTAAGATA
31 3563 TgcaACTACA        CCTATAATACAcTTAAAAGGTGATGCAAATAtaTTAAAATGTTTAAGATA
18 3668 TaacACTAC        gCCTATAATACAtTTAAAAGGTGAcagAAAcAgtTTAAAATGTTTAcGgTA

con     TaacacTaCagctacgCCtATAgT-CAttTaaAAGGTGAttcaAAtagtTTAAAaTGTTTaaGaTAta
                               JJ20-catttaaaaggtgaNtcNaatagtttaaaatgtttaagatata
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 6 3630 GgCTaAATGACAgAcAcAgACATTTaTTTGAtTTAatATCaTCAACGTGGCAcTGGGCCTCctCaaAG
        | || ||||||| | | | |||||| ||||| |||  ||| |||||||||| ||||||||  |  ||
11 3627 GaCTgAATGACAaATATAAACATTTGTTTGAaTTAgcATCtTCAACGTGGCATTGGGCCTCacCtgAG
           |      |||||| | |||| |    |      || || || ||||||||| ||       |
33 3621  cAGATTaAAAcctTATAAAgAgTTGTATAgTTCtaTGTCaTCcACcTGGCATTGGACCaGtgAcAAc
         ||||| |||     ||     ||||||| | |  |||| || || |||||||||||  |  | ||
16 3663  TAGATTtAAAAAgcATtgtacATTGTATAcTgCAGTGTCgTCTACATGGCATTGGACAgGacAtAAT
         |||  |    |||  ||     |||||||      |||||| ||||||||||||||||| |     ||
31 3623  TAGgcTGtcAAAAtATAaacAATTGTATgaAcAAGTGTCATCTACATGGCATTGGACAtGtacagAT
          ||  ||  |||| |||    |     |||  | |  | ||||| || |||||||||||
18 3728  cAGatTGcgAAAAcATAgcgAccacTATagAgAtaTaTCATCcACcTGGCATTGGACA    ggtgc

con     g-agattt-aaaaa-Ata-aca-ttgTaT-a-t-a-t-TCaTC-AC-TGGCAtTGGaC-tg-cc-aa-
        gcagatt-JJ20

 6 3698 GCACCACATAAA cATGCcATTGTAACtgTAACAT   ATgatAGTGAGGAACAAaGgCAaCAgTTTT
        |||||||||||  |||| ||||||||  ||||||    ||   ||||||||||| | || || ||||
11 3695 GCACCACATAAAA ATGCAATTGTAACatTAACAT   ATAgcAGTGAGGAACAACGtCAgCAaTTTT
           |       ||||| ||| |||||||||  ||||||        |       || ||||||    |    ||||
33 3688 aaAAAtagTAAAA ATGgAATTGTAACtgTAACATtTGtaAcTGAAcAGCAACAAC   AaatgTTTT
          |||    |||||  || |||||| ||  | |||| ||   | ||||  |||||        |   ||||
16 3730 GtAAAACATAAAA gTGCAATTGTtACacTtACATATGatAGTGAATgGCAAC    GtGACcAaTTTT
        | |||||||||||  ||| ||||| ||  | ||||||    |||  ||  |||      | ||| | ||||
31 3690 GGAAAACATAAAAA TGCtATTGTaACctTAACATATataAGTacATCACAA    AGAGACgAtTTTT
          |  ||    |||||  |  ||  | ||  |||||||      |||  | |||||    |||   | ||||
18 3791 aGgcAAtgaAAAAAcaGgaATacTgACtgTAACATAccatAGTgaAaCACAA    AGAacaaAaTTTT

con     g-a-aacatAAAaaatGcaATtgTaACtgTaACATatgatagt-aa-agcAAcaaag--aacaaTTTT

 6 3762 TAgAtgtTGTAAAAATACCcCCtACCATTAGcCA cAAacTGGGaTTTATGTCAcTgCAccTATTGTA
        || |   ||||||||||| || |||||||| ||  ||  |||| ||||||||| | ||  |||||||
11 3759 TAaAcAgTGTAAAAATACCACCcACCATTAGgCAT AAGgTGGGgTTTATGTCAtTaCATTTATTGTA
        ||    |  ||||||||||||||   |  |    || |||               | |  ||||||
33 3752 TAggTAccGTAAAAATACCACC tACTgTgcaAAT AAG                TACTGGATTTAT
        |    |   || |||||||||     ||| |   | |                   |||||||||||
16 3794 TgtcTcaaGTtAAAATACCA AAaACTaTtaCAGT      GTC           TACTGGATTTAT
        |    |   || ||||||||  || ||  |  ||||     |||                 |||||
31 3754 TAAATACTGTaAAAATACC tAAcACagTatCAGT      GTCaacaggatatatgactATTTA
        ||||||||||
18 3856 TAAATACTGT

con     TaaatactGTaaaaataccaccaaaca-tagcaat-aaggtcgg-tttatgt-actg-atttattgta

 6 3829 AtttgtatatatgtaaAtgtgTaaATATATGgTATtgGTGTAatacaActgTACaTGTATGGAaGTgG
        |                |    |  ||||||| |||  |||||     |   ||| |||||||| || |
11 3826 A          cCATTAcaccTgtATATATG TATAtGTGTA  CATAACATACgTGTATGGAgGTaG
                    |||||                       || |||||  ||| |||  |    ||||
33 3801         G aCATTA                   TAaGTGTA  CATcACAagCcaaTATG
                |
16 3843         G                                                     tCt
                                                                       |
31 3812                                                               gCc
                                                                       |
18 3866                               tgcaattccagatagtgtacaaatattggtgggataCa

con     a--------g--catta----t--atatatggtatatgtgta--cataacaaacatgtatggaagtcg
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 6 3897 TGCCTGTACAAATaGCTGCAGgAACAACcAgcACATTcATAcT       GCCTGTTaTaATTGCAT
11 3881 TGCCTGTACAAATTGCTGCAGcAACAACTAcAACATTGATATT       GCCTGTTGTTATTGCAT
33 3833             TGCTGC TaAtTgtATAtAACcATGATATTtgTTTTTG taTTaTGTTTTaTaTT
16 3847 atATGA caAAtcTtgatacTgcATccAcAaCATTAcTGgcgTGCTTTTTG  CTTTGCTTT GTGTG
31 3815 TaATGATtgAActaAatattTcTAcagtaAgCATT gTGCtaTGCTTTTTG  CTTTGCTTTTGTGTG
18 3904 TgAcaATgtAAtacAtatgcTgTAgtaccAatATgttatCacTtaTTTTTtatTTTGCTTTTGTGT

con     tgac-atacaa-ttgctgc-tgaacaaccA-cA--tt-ata-Tgcttttggccttt-cTtttgtgtt
                   O21-CTGCAGGAACAACCAGCACATTCATACT       GCCTGTTATAATTGCAT

 6 3957 TTGttGTATGTtTTgTTAGcATcaTACTTATtgTATggATATCTGAgTTTaTtGTgTAcACATCTGTG
11 3941 TTGcaGTATGTaTTcTTAGtATtgTACTTATaaTATTAATATCTGAtTTTgTaGTaTATACATCTGTG
33 3886 gT    TTTtaTGctTaTcCtTATTAtTACGTCCtTTAATAcTTTCcaTTTCTACcTATgCtTggTTG
16 3911 CT    TTT GTGTGTCTgCcTATTAATACGTCCgCTgcTttTGTCTGTGTCTACATAcaCATCATTA
31 3880 CTactaTTT GTGTGTCT     tgTcATACGTCCaCTtgTgcTGTCTGTGTCggtATAtgCAaCAcTA

18 3971

con     -tgctgtttg-tgtgt-tgcat--ta-tacgtccatt-atattttct-tttctgtatatacatc--tg
    O21-TTGTTGTATGTTTTGTTAGCATCATACTTATTGTATGGATATCTGAGTTTATTGTGTACACATCTGTG-O21

 6 4025 CTaGTACTAACACTgCTTTTATATTTaCTaTTGTGGCTgcTATTAACAACCCCcTT GCAATTtTTcc
11 4009 CTGGTACTAACACTTCTTTTATATTTGCTTTTGTGGCTttTATTAACAACCCCTTT GCAATTcTTTT
33 3950 CTGGT  gTTGGTATTgcTgcTtTggGtgTTTGTGG             gAtCtCCTTTaaaAATT TTTT
16 3974 aTAaT  ATTGGTATT                       acTaTTgTGGaTAACaGCAgCCTCTgCgTTTaG
31 3943 cTAtT  ATTaaTtgT                       gaTtTTaTGGgTtAttGCAaCCTCTcCaTTacG

18 3971

con     ctagtac-tt-atttttttatatttgcttttgtggcttttatgaa-aac-cc-ttc-caattttt--
    O21-CTAGTACTAACACTGCTTTTATATTTACTATTGTGGCTGCTATTAACAACCCCCTT GCAATTTTTCC-O21
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 6 4092  TACTAACtCTactTGTGTGtTAcTgTCCcGCaTTgTATATACACtacTAtATTGT      taccacA
11 4076  TACTAACaCTgtgTGTGTGCTATTTTCCTGCcTTTTATATACACataTACATTGTgcaaacgcAAcaA
33 4005  T          ~    tTGCTATTT  GTTgtTTTTATAT tTA    CCAaTGaTgTgtATtAATtt
16 4021  gTGTTTtaTTGTATATATtaTATTT  GTT     TATA   TA     CCATTATTTTTAATaCATAC
31 3990  tTGTTT  TTGTATATAT  gtTgT  GTT     TATA   TAtattCCATTATTTgTAATtCATAC
18 3971
con      tactaacactgtatat-tgctattttcgttc-ttttatatactata-tccattgtttttaat-cata-
     021-TACTAACTCTACTTGTGTGTTACTGTCCCGCATTGTATATACACTACTATATTGT      TACCACA-021

 6 4154  cAgcaaTGATGcTAACaTGTCAaTTtAATGATGGaGAT  ACcTGGcTGggTtTGTGGTTGTTatgTG
11 4144  TAATGgTGATGtTAACcTGTCACTTaAATGATGGtGAT  ACATGGtTGTtTcTGTGGTTGTTtacTG
33 4051  TCATGCACAgcaTAtgacacaACaagAgTAATGTATAT  ACATGtaTaTATTGTTtGTATATAtgTG
16 4075  ACATGCAC      gcTTTTTAAttacaTAATGTATATGTACATAaTgtaATTGTT ACATATA
31 4044  ACATGCA      tctTTTTTAA               GTCAAcAgTaaCTTTTTT AC
18 3971                       AtgcatgtatgtgtgctGcCAtgtcccgCTTTTgccAtctgtctgta

con      -catgcacatg-taac-t-t-Aattaaataatggagatgtacatggttg-tTtt-tg-t-t-tatgtg
     021-CAGCAATGATGCTAACATGTCAATTTAATGATGGAGAT  ACCTGGCTGGGTTTGTGGTTGTTATGTG-021

 6 4220  CcTTTaTTGTAGggaTgtTgGGgTTaTTaTT     gaTgCAcTAtAGaGCTGTACAaGGggaTaAAc
11 4210  CATTTgTTGTAGcTGTacTtGGATTGTTGTT     acTaCATTAcAGgGCTGTACATGGTacTgAAA
33 4117  CA   caTGGTGgTGTtTTAacATTGTTGTT      gTTATTTT     AgtTTTTTTTTTTTTGTA
16 4132     atTgTTGTATACcaTaActtactaTtTTtctTtTTTATTTcaTatAtaaTTTTTTTTTTGT
31 4081       TtGTGTATAC                    TgTTgtTTgTatTgGTattggTaTTggTaTTgg
18 4018  tgtgtgcGTaTgcAtgggtattggtatttgtgtatatTgtggTaataacGTcccctgccacagcaTtc

con      cattt-tt-gtg-a-t-ttag--tt-tt-tt-t-tt-ttt-ttt--a--g-t-t-tttttt-ttt-t-
     021-CCTTTATTGTAGGGATGTTGGGGTTATTATT     GATGCACTATAGAGCTGTACAAGGGGATAAAC-021

 6 4283  AcACcAAATGTaagAAGTGTAA  CAAAC aCAActgTAaTGatGATTATGTaacTATGcattATacT
11 4273  AaACTAAATGTgctAAGTGTAAATCAAACcgCAAtacTAcTGTgGATTATGTGTATATGtcacATggT
33 4171  ttACTAA            TAAAT         AccTTTATaTttagcaGTGTAT
16 4196                        TTgTTTgtTTgTTTTTTA
31 4124  tattggTATtggTaTaaTaaacTTTTTTaCTTtTTTTTTA
18 4086  acagtaTATgtaTtTtgTttttTaTTgccCaTgTTacTattgcatatacatgctatattgtctttaca
con      a-actaaatgtattaagtgtaatt-t--cc-t--tttT-atgttgattaagtgtatatg---tatact
     021-ACACCAAATGTAAGAAGTGTAA  CAAAC ACAACTGTAATGATGATTATGTAACTATGCATTATACT-021
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 6 4348 acTgATGGtGATTAT   aTaTAtATGAAtTAGAGTAAACCgTTTTTTATAtttgtaacaGTGTAtGc
          | |||| ||||||    | || ||||| ||||||||||| |||||||||         ||||| |
11 4341 gaTaATGGaGATTATG   TgTAcATGAAcTAGAGTAAACC TTTTTTATAcagtgtgtgGTGTAcGt
                  ||||||
33 4206          tATTATG

16 4214                                                       ataaactgTTATTA
                                                                      ||||||
31 4164                                                               TTATTA
                                                                       |  |
18 4154 gtaattgtataggttgttttatacagtgtattgtacattgtatattttgttttataccttttaTgcTt

con     g-taatggagattatg---tatacatgaa-tagagtaaacc-tttttatatt-ttaat-gt-tatt-
    O21-ACTGATGGTGATTAT   ATATATATGAATTAGAGTAAACCGTTTTTTATATTTGTAACAGTGTATGC-O21

 6 4413 TttgTATAccATggcacAtagTAGGGCcCGacGACGcAAgCGTGCGTCAGCtACACAgCTATATCAAA
        |   ||||  ||     |   |||||| ||  |||| || ||||||||||| ||||| ||||||||||
11 4405 TagtTATA tATAatgAAACcTAGGGCACGcaGACGtAAaCGTGCGTCAGCcACACAACTATATCAAA
                  | |   ||||      || |  |     | ||||| || || ||||||||||| ||||
33 4213           AGACACAAACGaTCTaCAAGgCGCA   AgCGTGCATCtGCaACACAACTATAcCAAA
                   |||||||||| ||| |||  ||||   | |||||||| || || ||||| ||  |||
16 4228 CttaacaATGCGACACAAACGtTCTgCAAAACGCACaAAACGTGCATCgGCTACcCAACTtTATaAAA
        |      |||||   |||||| ||| |||||||||| |||||||| || ||||| ||| | ||| |||
31 4170 C     cATGCGgtcCAAACGcTCTaCAAAACGCACTAAACGTGCgTCtGCTACaCAATTaTATcAAA
                |  |    ||| |      |   | |  |                     |
18 4222 tttgtattTttGtaatAAAaGtatggtAtccCaCcgTgccgcacgacgcaaacgggctTcggtaactg

con     tttgtatat-aga-acaAacgt-c-gcaagacgc-gtaaacgtgc-tc-gctacacaactatatcaaa
    O21-TTTGTATACCATGGCACATAGTAGGGCCCGACGACGCAAGCGTGCGTCAGCTACACAGCTATATCAAA-O21

 6 4481 CATGtAAactCACTGGaACATGcCCCCCAGATGTAATTCCTAAgGTgGAgCAcAacACcATTGCAGAT
        |||| ||   |||||| ||||| |||||||||||||||||||| || || || |  || |||||||||
11 4472 CATGCAAGGCCACTGGtACATGtCCCCCAGATGTAATTCCTAAAGTtGAACAtAcTACtATTGCAGAT
        ||||||||||||| || || || || || ||||| ||||||||||| |||   | ||| || ||||||
33 4268 CATGCAAGGCCACAGGcACcTGcCCACCcGATGTTATTCCTAAAGTgGAAGGaAgTACcATaGCAGAT
        |||||||     |||| || || ||||| ||  |||| ||||| || ||||| |  || || || ||
16 4296 CATGCAAAcagGCAGGTACaTGTCCACCtGACaTTATACCTAAgGTtGAAGGcAaaACtATTGCtGAa
        |||| |||   |||||||| |||||| | ||| ||||||||||  | |||   |  || ||||| ||
31 4233 CATGtAAAgcAGCAGGTACtTGTCCAtCaGACgTTATACCTAAaaTaGAACaTActACcATTGCaGAC
          |   |   | || |||      |         |  |||| |  | |  | ||        |    |
18 4290 acTtatAtaaAaCAtGTAaacaatCtggtacatgTccACCTgAtgTtGttCcTAaggtggagGgcacC

con     caTgcaAagccaCagGtAcatgtcCaccagatgttat-CCTaAagTtGaacatAataccattGcagat
    O21-CATGTAAACTCACTGGAACATGCCCCCCAGATGTAATTCCTAAGGTGGAGCACAACACCATTGCAGAT-O21
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 6 4549 CAAATATTAAAATGGGGAAGtTTgGGGGTgTTTTTTGGaGGGTTgGGTATaGGcACgGGttCcGGcAc
        |||||||||||||||||||| || ||||| |||||||| ||||| ||||| || || ||  | || |
11 4540 CAAATATTAAAATGGGGAAGcTTAGGGGTTTTTTTTGGTGGGTTAGGTATTGGtACAGGggCTGGTAg
        |||||  | ||||  || || |||||||||||||||||||| ||||||||||| |||||  |||||
33 4336 CAAATtcTtAAATATGGcAGTTTAGGGGTTTTTTTTGGTGGtTTAGGTATTGGcACAGGcTCTGGTtC
        |||||  |  ||||||| ||| | || || ||||||||||| ||||| ||||| ||||| || ||| |
16 4364 CAAATATTAcAATATGGaAGTATGGGTGTaTTTTTTGGTGGGTTAGGaATTGGaACAGGgTCgGGTAC
        |||||||||   ||||| ||||||||||| |||||||||||||| || |||||  | || || |||||
31 4301 CAAATATTAaggTATGGtAGTATGGGTGTtTTTTTTGGTGGGTTgGGtATTGGgtCcGGCTCtGGTAC
            ||  |    |           |        |||||   ||      |||    |||   |||||
18 4358 acgtTAgcAgataAaatattgcaatGgtcaagccTTGGTataTTtttgggTGGacttGGCataGGTAC

con     caaaTattaaaatatggaagttt-gGggtttttTTGGtgggTTaggtattGG-acaGGctctGGtac
    O21-CAAATATTAAAATGGGGAAGTTTGGGGGTGTTTTTTGGAGGGTTGGGTATAGGCACGGGTTCCGGCAC-O21

 6 4617 TGGgGGTCGTaCtGGcTATgTtCCCTTacaAActTCTgCaAAaCCTtCTATTACTaGtGGGCCtatgG
        ||| |||||| | || ||| | |||||   ||  ||| | || ||| |||||||| | |||||    |
11 4608 TGGcGGTCGTgCaGGgTATaTACCCTTgGGAAgcTCTCCcAAgCCTGCTATTACTgGgGGGCCagCaG
         || ||  |  | || ||| ||||  | || |     ||     | |||   |       ||   |
33 4404 AGGtGGAaGgACTGGcTATgTACCtaTtGGtACtgacCCaCCtACAGCTgCAAtccCctTGCagCCTa
        ||| ||| | ||||| ||| | ||  | || ||    || || |||||| ||    |  |    |||
16 4432 AGGcGGACGCACTGGgTATaTtCCatTgGGaACAaGgCCTCCcACAGCTaCAGAtaCAcTTgctCCTg
         || || |||||||| ||| | ||  |  | ||| | ||| | ||||   | ||  ||  |   |||
31 4369 TGGgGGTCGCACTGGaTATgTcCCtcTtaGtACACGtCCTtCTACAGtaTCtGAggCAagTaTaCCTa
        |||  || | || ||   |    |       |  |       |      ||  |  ||    |   |
18 4426 TGGcaGTgGtACaGGgggTcgtaCagggtacAttCcattgggTgggcgtTCcaAtaCAgtggTggaTg

con     tGGcgGtcGtaCtGGgtaTgttcC-ttgggaAct-ctcc--ctacagctactaatacag-gcc-cctg
                                BE11-GAAGCXCXCCCAAGCCXGCXAXX-BE11
                   BE12-TATATACCCTTGGGAAGCXCXCCCAAGCCXGCXAX-BE12
    O21-TGGGGGTCGTACTGGCTATGTTCCCTTACAAACTTCTGCAAAACCTTCTATTACTAGTGGGCCTATGG-O21

 6 4685 CtCGTCCtCCtGTGgTgGTGGAGCCTGTgGCCCCTTCgGATCCaTCtATTGTGTCtTTAATTGAaGAa
        | ||||| || ||| | |||||||||||| ||||||| ||||| || |||||||| ||||||||| ||
11 4676 CACGTCCgCCaGTGcTTGTGGAGCCTGTTGCCCCTTCcGATCCcTCcATTGTGTCcTTAATTGAgGAg
         |||||| || ||   ||| ||  ||||||  ||||  ||  | || || ||||| ||||| || ||
33 4472 TACGTCCtCCgGTtACTGTAGAcaCTGTTGGaCCTTtaGActCgTCTATAGTGTCaTTAATaGAAGAA
        || | || ||  | || |||||  |||| || ||||  ||  | |||||||| || ||| | ||||||
16 4500 TAAGACCcCCttTaACaGTAGAtCCTGTgGGcCCTTctGAtCCtTCTATAGTtTCTTTAGTgGAAGAA
        | ||||| ||  | |   | || ||||| || || |  ||  || ||||||||   | | || ||||||
31 4437 TTAGACCaCCAgTTAgCaTtGAcCCTGTaGGtCCcTTGGACCCCTCTATAGTAagTcTTGTTGAAGAA
        || | ||  ||  |  |   |    | | |  ||  ||| |||| |       |  | |||||  |  |
18 4494 TTgGtCCtaCAcgTccCccaGtggtTaTtGaaCCtgTGGgCCCCaCagacccAtcTaTTGTTacAttA

con     t-cGtCCtcCagttac-gtaGagccTgTtGgcCCtt-gGa-cCctCtatagtgtcttTa-Ttgaagaa
     BE26-CGXCCXCCGGXXACXGXAGAxA-BE26      JJ22-TCTATTGTGTCNTTAATNGAAGAA
      BE27-GXCCXCCGGXXACXGXAGACACX-BE27 O22-GGATCCATCTATTGTGTCTTTAATTGAAGAA
       BE28-XCCXCCGGXXACXGXAGACACXGXXGGACCXXXAG-BE28
    O21-CTCGTCCTCCTGTGGTGGTGGAGCCTGTGGCCCCTTCGGATCC-O21
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  6 4753  TCgGCaATcATTAAcGCaGGgGCgCC      TGAaaTtGTgCCCCC   TgCACAcGGTGGgTTTAC
 11 4744  TCtGCTATTATTAAtGCtGGTGCACC      TGAggTgGTaCCCCC   TACACAgGGTGGcTTTAC
 33 4540  ACaAGTTTTATaGAgGCaGGTGCACCA      GccCCaTCtATTCC   TACACcATCAGGtTTga
 16 4568  ACTAGTTTTATTGATGCTGGTGCACCAaCatCTGtaCCtTCcATTCCcCCagatgtATCAGGaTTTag
 31 4505  tCTGGaaTTgTTGATGTTGGTGC   ccCTGCTCCTAtaCCacacCCTCCTacaACATCTGGGTTTGA
 18 4562  ataGaggactccagTGTgGtTaCatcaggTGCaCCTAggCCtacgttTaCTggcACgTCTGGGTTTGA

con       -ctggtattatt-atGctGgtgCacca-ctgctgc-at--c--cccctcct-caccatctGGgTTT-a
          TCTAGTNTTATTAATGCAGGTGCACC-JJ22
                 BE5-CAXXAACGCAGGGGCGCC------XGAA-BE5
           BE6-GGCAAXCAXXAACGCAGGGGCG-BE6
            BE7-GCAAXCAXXAACGCAGGGGCGCC------XGAAAXXGXGCC-BE7
                                     O5-GTACCCCC   TACACAGGGTGGCTTTAC
      O22-TCGGCAATCATTAACGCAGGGGCGCC      TGAAATTGTGCCCCC   TGCACACGGTGGGTTTAC-O22

  6 4812  aATtACATCcTCTGAAaCaACTACcCCTGCaATaTTgGATGT   aTCaGTT   ACtAgTCACACTA
 11 4803  TATaACATCATCTGAAtCgACTACACCTGCtATTTTaGATGT   gTCTGTT   ACcAaTCACACTA
 33 4599  TgTTACTACATCTGCAGATACTACACCTGCaATTATTAATGTttcaTCTGTTggggAgtcatCTATTc
 16 4636  TATTACTACtTCaaCtGATACcACACCTGC tATATTA           GATattaAtAatACTGTTA
 31 4570  cATTgCTACaaCtGCaGAcACaACACCTGC aATTTTA           GAT   gtaACaAgTGTTA
 18 4630  tATaaCatCtgCgGgtacaACtACACCTGCggtTTTggatatcacaccttcgtctacctCtgtgtcTA

con       taTtaC--CatCtgcag--ACtACaCCTGCaatttTt-atgt--catctgtt--tac-act--ta-Ta
       O5-TATAACATCATCTGAATCGACTACACCTGCTATTTTAGATGT   GTCTGTT   ACCAATCACACTA-O5
      O22-AATTACATCCTCTGAAACAACTACCCCTGCAATATTGGATGT   ATCAGTT   ACTAGTCACACTA-O22

  6 4874  CtACTA   GTaTaTTTagAAATCCtgTcTTTACAGAACCtTCTGTAAcACAaCCCCAACCACCcGTG
 11 4865  CcACTA   GTgTgTTTcaAAATCCCcTgTTTACAGAACCgTCTGTAATACAgCCCCAACCACCTGTG
 33 4667  aaACTATTtCTACACATttAAATCCCACaTTTACTGAACCATCTGTAcTACAcCCTCCAgCgCCTGCA
 16 4692  ctACTgTTaCTACACATaAtAATCCCACTTTcACTGAcCCATCTGTATTGCAGCCTCCAACACCTGCA
 31 4623           gCACACATgAaAATCCTACTTTTACTGATCCATCTGTATTGCAGCCTCCtACACCTGCA
 18 4698  tttccacaacCAatttTaccAATCCTgCaTTTtCTGATCCgTCcaTtaTtgAagtTCCacaAaCTGgg

con       ctactatta-taca--TaaaAATCC-ac-TTtaCtGAaCCaTCtgTaatacAgcctCcaccacCtGc-
       O5-CCACTA   GTGTGTTTCAAAATCCCCTGTTTACAGAACCGTCTGTAATACAGCCCCAACCACCTGTG-O5
      O22-CTACTA   GTATATTTAGAAATCCTGTCTTTACAGAACCTTCTGTAACACAACCCCAACCACCCGTG-O22
                                                                     O27-CTGCA
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 6 4939 GAGGCtAaTGGaCAtATAtTaATtTCTGCaCCcACtgTAACgTCaCAcCcTaTAGAgGAaATTCCttT
11 4930 GAGGCCAgTGGtCAcATAcTtATaTCTGCCCCaACaaTAACaTCcCAACaTgTAGAAGACATTCCAcT
33 4735 GAAGCCtcTGGaCATTTTATAtTTTCTTCCCCtACTgTTAGcACACAAAgTTATGAAaACATaCCAAT
16 4760 GAAACtggAGGgCATTTTAcACTTTCATCATCcACTATTAGtACACATAATTATGAAGAAATtCCTAT
31 4682 GAAACatCAGGTCATTTAcTACTTTCATCATCatCTATTAGcACACATAATTATGAGGAAATACCTAT
18 4766 GAggtggCAGGTaATgTAtTtgTTggtaCccCtaCatcTgGaACACATgggTATGAGGAAATACCTtT

con      GA-gc--c-GGtcAttTa-ta-TttcttC-cC-aCtattag-aCaCAtaattatGA-gAaAT-CCtaT
     O5-GAGGCCAGTGGTCACATACTTATATCTGCCCCAACAATAACATCCCAACATGTAGAAGACATTCCACT-O5
    O22-GAGGCTAATGGACATATATTAATTTCTGCACCCACTGTAACGTCACACCCTATAGAGGAAATTCCTTT-O22
    O27-GAAGCCTCTGGACATTTTATATTTTCTTCCCCTACTGTTAGCACACAAAGTTATGAAAACATACCAAT-O27

 6 5007 AGAtACTTTTGTgGTATCaTCTAGTGATAGcGGtCCTACATCCAGTACcCCTgTTCCTgGTaCTgcaC
11 4998 AGAcACTTTTGTTGTATCCTCTAGTGATAGTGGaCCTACATCCAGTACtCCTcTTCCTcGTgCTtttC
33 4803 GGATACcTTTGTTGTTTCCACAgACagTAGTAatGTAACATCaAGCACgCCCATTCCAGGGTCTCGCC
16 4828 GGATACATTTATTGTTagCACAAACccTAAcAcaGTAACtAGTAGCACACCCATaCCAGGGTCTCGCC
31 4750 GGATACATTTATTGTTTCTACTAAtaaTGAaAAcaTAACaAGTAGCACACCCATtCCAGGGGTGCGCC
18 4834 acAaACATTTgcTtcTTCTggTAcggggGAggAacccAttAGTAGtACcCCatTgCCtactGTGCGgC

con      -gAtACaTTTgttgtttccactaatgata---aac-aAca--tAG-AC-CCcaTtCC-gg-gctcgcC
     O5-AGACACTTTTGTTGTATCCTCTAGTGATAGTGGACCTACATCCAGTACTCCTCTTCCTCGTGCTTTTC-O5
    O22-AGATACTTTTGTGGTATCATCTAGTGATAGCGGTCCTACATCCAGTACCCCTGTTCCTGGTACTGCAC-O22
    O27-GGATACCTTTGTTGTTTCCACAGACAGTAGTAATGTAACATCAAGCACGCCCATTCCAGGGTCTCGCC-O27

 6 5075 CTCGGCCTCGtGTGGGccTaTATAGTCGTGCaTTgCAcCAGGTgCAGGTTACaGACCCtGCaTTTcTt
11 5066 CTCGGCCTCGgGTGGGTTTgTATAGTCGTGCcTTaCAgCAGGTACAGGTTACgGACCCcGCgTTTTTg
33 4871 CTGTGGCACGCCTtGGTTTATATAGTCG       CAAtACcCAACAGGTTA AGGTTGTtGACCCTGC
16 4896 CaGTGGCACGCCTAGGaTTATATAGTCG       CACaACACAACAGGTTA AAGTTGTaGACCCTGC
31 4818 GTcctGCACGTtTAGGgTTATATAGT       AaGGCtACACAACAAGTaA AAGTTaTTGAtCCaaC
18 4902 GTgtaGCAgGTccccGccTtTAcAGT       AgGGCctacCAACAAGT gtcAGTggcTaAcCCtga

con      ct-tggCacGtct-gG-tTaTAtAGTcgtgc-atg---a--caaCAgGTtaca-gttgttga-cctgc
     O5-CTCGGCCTCGGGTGGGTTTGTATAGTCGTGCCTTACAGCAGGTACAGGTTACGGACCCCGCGTTTTTG-O5
    O22-CTCGGCCTCGTGTGGGCCTATATAGTCGTGCATTGCACCAGGTGCAGGTTACAGACCCTGCATTTCTT-O22
    O27-CTGTGGCACGCCTTGGTTTATATAGTCG       CAATACCCAACAGGTTA AGGTTGTTGACCCTGC-O27
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 6 5143 TCCACtCCtCAaCGcTTaaTtACaTAT         GAtAACCCTGTaTATGAA        GGgGAgGATG
11 5134 TCCACgCCaCAgCGaTTggTAACTTAT         GAcAACCCTGTcTATGAA        GGaGAaGATG
33 4932 TTTTtTAACatCgCCTcaTAAACTTATaACATATGATAATCCTGCATtTGAAaGctTtGAccctGAaG
16 4957 TTTTgTAACcaCTCCcAcTAAACTTATTACATATGATAATCCTGCATATGAAgGTaTAGATGtgGAta
31 4879 GTTTCTTAgtgCTCCAAaacAgCTAATTACATATGAaAACCCTGCcTATGAAacTgTAaATGCtGAaG
18 4963 GTTTCTTAcacgTCCAtcctcttTAATTACATATGAcAACCC                     gGCctttG

con     ttttct-accactcctta-taacttATtacatatGAtAAcCCtgcatatgaaagt-taga-gc-gatg
    O5-TCCACGCCACAGCGATTGGTAACTTAT         GACAACCCTGTCTATGAA        GGAGAAGATG-O5
   O22-TCCACTCCTCAACGCTTAATTACATAT         GATAACCCTGTATATGAA        GGGGAGGATG-O22
   O27-TTTTTTAACATCGCCTCATAAACTTATAACATATGATAATCCTGCATTTGAAAGCTTTGACCCTGAAG-O27

 6 5198 TtAGTgTACAATTTAgtCATGAtTCTA        TaCACAATGCACCTGATGAgGCtTTTATGGAcATa
11 5189 TaAG¯PTACAATTTAccCATGAgTCTA        TcCACAATGCACCTGATGAaGCaTTTATGGATATT
33 5000 AcACATTACAATTTcaaCATAgTGATA        TatcaccTGCTCCTGATCCTGACTTTcTaGATATT
16 5025 AtACATTATAtTTTTCtagTAaTGATAatagtaTTAATATAGCTCCaGATCCTGACTTTtTgGATATa
31 4947 AatCTTTATACTTTTC       caATAcatCgCaTAATATAGCcCCTGATCCcGACTTTcTaGATATT
18 5013 AgcCTgTggACacTaCattaacattTgatcCtCgTAgTgatGttCCTGATtCaGAtTTTaTgGATATT

con     a-actttTacAattTac-cataattaTaat-ctcttaataatGctCCtGATcc-GacTTTaTgGAtATt
    O5-TAAGTTTACAATTTACCCATGAGTCTA        TCCACAATGCACCTGATGAAGCATTTATGGATATT-O5
   O22-TTAGTGTACAATTTAGTCATGATTCTA        TACACAATGCACCTGATGAGGCTTTTATGGACATA-O22
   O27-ACACATTACAATTTCAACATAGTGATA        TATCACCTGCTCCTGATCCTGACTTTCTAGATATT-O27

 6 5260 ATTcGttTgCAcAGACCtGCcATtgCGTCCcGACGtGGcCTTGTGCGgTacAGTCGCATTGGaCAACG
11 5251 ATTaGAcTACATAGACCaGCTATaACGTCCaGACGgGGTCTTGTGCGTTTTAGTCGCATTGGgCAACG
33 5062 ATTGCATTACATAGGCCtGCTATtACaTCTcGtaGacaTacTGTGCGTTTTAGTAGAgTaGGTCAAAA
16 5093 gTTGCtTTACATAGGCCaGCatTaACCTCTaGgcGtAcTggcaTTAGgTAcAGTAGAaTtGGTAATAA
31 5009 ATaGCaTTACATAGGCCTGCccTtACCTCacGtaGgAacACTGTTAGaTATAGTAGAcTAGGTAATAA
18 5081 ATccgtcTACATAGGCCTGCttTaACaTCcaGgcGtgggACTGTTcGcTtTAGTAGAtTAGGTcAacg

con     aTtg--tTaCAtAGgCCtGCtaT-aC-TCc-G-cGtggtactgT-cG-T-tAGTaGaaT-GGtcAa--
      JJ24-TACATAGGCCTGCTATAACNTCCAGNCGTGGTNNTGTGCGNTTTAGTAGA-JJ24
    O5-ATTAGACTACATAGACCAGCTATAACGTCCAGACGGGGTCTTGTGCGTTTTAGTCGCATTGGGCAACG-O5
                                          O16-ACTGTGCGTTTTAGTAGAGTAGGTCAAAA-O16
   O22-ATTCGTTTGCACAGACCTGCCATTGCGTCCCGACGTGGCCTTGTGCGGTACAGTCGCATTGGACAACG-O22
   O27-ATTGCATTACATAGGCCTGCTATTACATCTCGTAGACATACTGTGCGTTTTAGTAGAGTAGGTCAAAA-O27
                                  O28-GTAGACATACTGTGCGTTTTAGTAGAGTAGGTCAAAA
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 6 5328 GGGGTCtATGcACACtCGCAGcGGAaAgCAcATAGGgGCCCGCATtCATTATT
11 5319 GGGGTCcATGtACACaCGCAGTGGAcAACAtATAGGtGCCCGCATACATTATT
33 5130 AGccACACTtaAaACTCGCAGTGGtAAACAaATtGGaGCTAGaATACATTATTATcAgGATTTAAGTc
16 5161 ACAAACACTaCGtACTCGTAGTGGaAAAtCTATaGGTGCTAaGGTACATTATTATTATGATTTAAGTA
31 5077 ACAAACTtTGCGcACTCGTAGTGGTgCtaCTATtGGTGCaAGGGTgCATTATTATTATGATATtAGTA
18 5149 ggcAACTaTGtttACcCGcAGcGGTaCacaaATaGGTGCtAGGGTtCAcTtTTATcATGATATaAGTc

con      -g-aaCtaTgcacACtCGcAGtGG-aaacatATaGGtGCtagg-TaCAtTaTTatcatgatataagta
     O5-GGGGTCCATGTACACACGCAGTGGACAACATATAGGTGCCCGCATACATTATT(-O5)
    O16-AGCCACACTTAAAACTCGCAGTGGTAAACAAATTGGAGCTAGAATACATTATTATCAGGATTTAAGTC-O16
    O22-GGGGTCTATGCACACTCGCAGCGGAAAGCACATAGGGGCCCGCATTCATTATT(-O22)
    O27-AGCCACACTTAAAACTCGCAGTGGTAAACAAATTGGAGCTAGAATACATTATTATCAGGATTTAAGTC-O27
    O28-AGCCACACTTAAAACTCGCAGTGGTAAACAAATTGGAGCTAGAATACATTATTATCAGGATTTAAGTC-O28

 6 5381           TTtAtGAtATTTCACCtaTTgCACAgGCTGCAGAaGAAATAGAAaTGCACC TCTtGTGG
11 5372           TTcAgGAcATTTCACCagTTaCACAAGCTGCAGAgGAAATAGAAcTGCACCCTCTAGTGG
33 5198 CTATTG    TgcCtttAGAcCACaccgTgCcAAATgaACAAtaTgAATtAcAgcCTttaCaTgAtacT
16 5229 CTATTGATCCTGCAGaAGAAAtagaatTACaAAcTatAacAccTtCtaCAtAtACTACcACTTCacaT
31 5145 gTATTaATCCTGCAGgtGAAAgTATTGAAaTGCAaCCTTTAGgggCgTCTGCaACTACtACTTCtacT
18 5217 cTATTgcaCCTtCcccaGAAtaTATTGAAcTGCAgCCTTTAG   taTCTGC         caCggag

con      ctattgatc-t-c---agaacacat--taca-aagct-caa--g-aatc--aa-ctaccc--tcg---
          (O5-)TTCAGGACATTTCACCAGTTACACAAGCTGCAG-O5
    O16-CTATTG   TGCCTTTAGACCACACCGTGCCAAATGAACAATATGAATTACAGCCTTTACATGATACT-O16
    O22-         TTTATGATATTTCACCTATTGCACAGGCTGCAG-O22
    O27-CTATTG   TGCCTTTAGACCACACCGTGCCAAATGAACAATATGAATTACAGCCTTTACATGATACT-O27
    O28-CTATTG   TGCCTTTAGACCACACCGTGCCAAATGAACAATATGAATTACAGCCTTTACATGATACT-O28

 6 5441 CTGCAcAggATGAtACaTTTGATATTTATGCTGAAtCtTTTGAaCCTggCatTaACCCTacCCAACAc
11 5432 CTGCAgAaaATGAcACGTTTGATATTTATGCTGAAcCATTTGAcCCTatCccTgACCCTgtCCAACAT
33 5263 tCtaCaTCgtCTtaTaGTATTAATgATGG   tTTgTATGATgTTTATGC          TgaCgAtGT
16 5297 gCAgCcTCacCTacTTcTATTAATaATGGA   TTaTATGATaTTTATGCaGATgacttTattACAGA
31 5213 ttAAATGAtggCTTaTaTGAcATTTATGCAGA   CAcTGATtTTaCTGTGGATacACCTgCcACAcA
18 5273 gacAATGA   CTTgTtTGAtATaTATGCAGAtgaCAtgGAcccTgCaGTGccTgtACCatCgcgttc

con      -t-aa--a-a---tat-T-ttAt-taTg-acag-ac-atgatatt--tgc---taccctt-ccaa---
    O16-TCTACATCGTCTTATAGTATTAATGATGG   TTTGTATGATGTTTATGC          TGACGATGT-O16
    O27-TCTACATCGTCTTATAGTATTAATGATGG   TTTGTATGATGTTTATGC          TGACGATGT-O27
    O28-TCTACATCGTCTTATAGTATTAATGATGG   TTTGTATGATGTTTATGC          TGACGATGT-O28
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 6 5509 cCTGTTACAaatatatcagAtaCaTATtTaACtTCCACACCTAATACagTTaCACAAcCGTGGGTAA
11 5500 tCTGTTACA          cAgtCtTATCTtACcTCCACACCTAATACCcTTtCACAAtCGTGGGTAA
33 5319 ggaTaaTgtAczCaCcccAAtgCaacaCTCATacAgtaCgTTtgCAaCaacaCgTACcaGcAATGTgt
16 5362 TAcTtcTaCAaCCcCggtAcCatctgtacCCTCtACatCTTTaTCAGgtTATaTTCCTgCAAATACaA
31 5278 TAaTgtTTCCcCTtCtacTgCTgtAcAgTCCaCatCTgCTgTgTCTGCCTATgTaCCTACAAATACCA
18 5338 TAcTaccTCCttTgCattTttTaaAtAtTCgcCcaCTatatctTCTGCCTcTtcctaTAgtAATgtaA

con     ta-tttt-ca---tctc--attca----tcacctac--c-ttatcagcct-tc-ca-tagtaatgtaa
      O16-GGATAATGTACACACCCCAATGCAACACTCATACAGTACGTTTGCAACAACACGTACCAGCAATGTGT-O16
      O27-GGATAATGTACACACCCCAATGCAACACTCATACAGTACGTTTGCAACAACACGTACCAGCAATGTGT-O27
      O28-GGATAATGTACACACCCCAATGCAACACTCATACAGTACGTTTGCAACAACACGTACCAGCAATGTGT-O28

 6 5577 cACCACAGTtCCATTGTCAcTtCCTAaTGACctGTTTtTaCAaTCTGGcCCTGAtATAACTTTTCCTA
11 5559 tACCACAGTcCCATTGTCAATcCCTAgTGACTGGTTTGTgCAGTCTGGgCCTGACATAACTTTTCCTA
33 5387 CtATACCTTTaaATacaGgATttgATAcTCCTGTTaTGTCtGGcCCTGATATACCtTccCcTTTAtTT
16 5430 CaATtCCTTTtgGTggtGcATacaATATTCCTtTAgTaTCaGGtCCTGATATACCcATtaATaTAaCT
31 5346 CtGTgCCacTAAGTaCaGgTTttGAcATTCCcaTATTtTCtGGgCCTGATgTACCtATagAgCATgCA
18 5406 CgGTcCCttTAAcctCctcTTggGAtgTgCCtgTATacaCgGGtCCTGAT  AttacattAcCATctA

con     ca-taCctttaaatt-tg-aTtcgatat-cCtgt-tt-tc-ggtCctGat-taccataacattt-cta
      O16-CTATACCTTTAAATACAGGATTTGATACTCCTGTTATGTCTGGCCCTGATATACCTTCCCCTTTATTT-O16
      O27-CTATACCTTTAAATACAGGATTTGATACTCCTGTTATGTCTGGCCCTGATATACCTTCCCCTTTATTT-O27
      O28-CTATACCTTTAAATACAGGATTTGATACTCCTGTTATGTCTGGCCCTGATATACCTTCCCCTTTATTT-O28

 6 5645 CTGCAcCTATGGGAACACCCTTTAGTCCTGTAACTCCTGCTTTACCTACAGGCCCTGTTTTcATTACA
11 5627 CTGCAtCTATGGGAACACCCTTTAGTCCTGTAACTCCTGCTTTACCTACAGGCCCTGTTTTTATTACA
33 5455 CcCacAtCTaGccCATTtgT      TCCTATttCgCCTttTTTTCCTtttGACACcATTgTTGTaGAc
16 5498 gaCcaAgCTccTTCATTAaT      TCCTATaGttCCagggTCTCCACAAtAtACaATTaTTGcTGAT
31 5414 CctaCACaGgtTTtCCCATT      TCCTtTGGCCCCTaCaaCgCCACAAgtGTCTATTtTTGTTGAT
18 5472 CtacCtCtGtaTggCCCATTgtatcaCCcacGGCCCCTgCctCtaCACA   GTaTATTggTaTacAT

con     ct-c-act-tgtg-ac-a-ttttagtCCtatagctCCtgctt-tcC-caag-c-ctaTTttt-ttgat
                  BE22-CCCAXXGXAXCACCCACGGCCC-BE22
                  BE23-CCCAXXGXAXCACCCACGGCCCCXGCCXCXACACA-BE23
      O16-CCCACATCTAGCCCATTTGT      TCCTATTTCGCCTTTTTTTCCTTTTGACACCATTGTTGTAGAC-O16
      O27-CCCACATCTAGCCCATTTGT      TCCTATTTCGCCTTTTTTTCCTTTTGACACCATTGTTGTAGAC-O27
      O28-CCCACATCTAGCCCATTTGT      TCCTATTTCGCCTTTTTTTCCTTTTGACACCATTGTTGTAGAC-O28
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 6 5713 GGTTCTGgaTTtTATTTGCATCCTgCATGGTAtTTTGCACGtAaACGCCGTAAACGTATTCCCTTATT
11 5695 GGTTCTGACTTcTATTTGCATCCTACATGGTAcTTTGCACGcAGACGCCGTAAACGTATTCCCTTATT
33 5518 GGTGCTGACTTTgtTTTACATCCTAGTTATTtATTTTACGtcGcaGgCGTAAACGTTTTCCATATTT
16 5561 GcaGGTGACTTTTATTTACATCCTAGTTATTAcATGTTACGAaaaCGACGTAAACGTTTACCATATTT
31 5477 GGgGGTGATTTTTATTTGCAcCCTAGTTATTATATGTTAaaAcgtCGACGTAAACGTGTAtCATATTT
18 5537 GGtacacATTaTTATTTGtggCCattaTATTATtTtaTtcctaagaaACGTAAACGTGTtcCcTATTT

con     GgtgctgacTtttaTTTgcatCCtag-TatTat-Ttttacgta-acgaCGTAAACGT-TtcC-TatTT
                                                  JJ25-CGTAAACGTNTTCCCTATTT
                                                       PCR2-CGTTTTCCATATTT
    O27-GGTGCTGACTTTGTTTTACATCCTAGTTATTTATTTTACGTCGCAGGCGTAAACGTTTTCCATATTT-O27

 6 5781 TTTTtCAGATGT       GGCGGCCTAGCGACAGCACAGTATATGTGCCTCCTCCtAACCCTGTATCC
11 5763 TTTTACAGATGT       GGCGGCCTAGCGACAGCACAGTATAT[illegible]GCCTCCTCCcAACCCTGTATCC
33 5586 TTTTACAGATGTCcgTgTGGCGGCCTAGTGAGGCCACAGTgTACcTGCCTCCT   GTaCCTGTATCT
16 5629 TTTTtCAGATGTCTCTtTGGCtGCCTAGTGAGGCCACTGTCTACTTGCCTCCT   GTCCCAGTATCT
31 5545 TTTTaCAGATGTCTCTGTGGCGGCCTAGcGAGGCTACTGTCTACTTaCCACCT   GTCCCAGTGTCT
18 5605 TTTTgCAGATGgCTtTGTGGCGGCCTAGtGAcaaTACcGTaTAtcTtCCACCT   ccttCtGTGgCa

con     TTTTaCAGATGtctctgtGGCgGCCTAG-GA--ccACaGTaTA--TgCCtCCTcc-gtccCtGTatCt
        TTTTNCAGATGTCTNTGTGGCGGCCTAGTGA-JJ25
        PCR1-CAGATGTCTCTGTGGCGGCCTAGTG-PCR1
        TTTTGCAGATG-PCR2
    O27-TTTTACAGATGTCCGTGTGGCGGCCTAGTGAGGCCACAGTGTACCTGCCTCCT   GTACCTGTATCT-O27

 6 5843 AAaGTTGTTGCCACGGATGCtTATGTTActCGCACCAACATATTTTATCATGCCAGCAGTTCTAGACT
11 5825 AAgGTTGTTGCCACGGATGCgTATGTTAaaCGCACCAACATATTTTATCATGCCAGCAGTTCTAGACT
33 5651 AAaGTTGTcAGCACtGATGAATATGTgtCtCGCACAAgCATtTATTATtATGCtGGtAGTTCCAGACT
16 5694 AAgGTTGTAAGCACGGATGAATATGTtgCACGCACAAACATATATTATCATGCAGGaAcaTCCAGACT
31 5610 AAAGTTGTAAGCACGGATGAATATGTaACACGaACcAACATATATTATCAcGCAGGCAGtgCTAGgCT
18 5670 AgAGTTGTAAatACcGATGAtTATGTgACtCccACaAgCATATtTTATCAtGCtGGCAGctCTAGatT

con     AaaGTTGTaagcACgGATGaaTATGTtac-CgcAC-AaCATaT-TTATcAtGC-gGcAgttCtAGacT
   JJ26-GTTGTNANCACGGATGANTATGTTACTCGCACAA-JJ26
   PCR3-AAGTTGTAAGCACCGATGAATATGT-PCR3
  LCR1A-AAGTTGTAAGCACGGATGAATATGT-LCR1A
                             LCR1B-TGCACGCACAAACATATATTATCA-LCRB
                            LCR1B'-ACGTGCGTGTTTGTATATAATAGTA-LCRB'
    O27-AAAGTTGTCAGCACTGATGAATATGTGTCTCGCACAAGCATTTATTATTATGCTGGTAGTTCCAGACT-O27
 6 5911 tCTTGCaGTGGGACATCCtTATTttTCcATaAAA    cggGcTAA    C      AAAA CtGTTGTgC
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11 5893 cCTTGCTGTGGGACATCCATATTacTCTATcAAAAA   aGtTAA    C      AAAA CAGTTGTAC
33 5719 tCTTGCTGTTGGcCATCCATATTTTTCTATTAAAAAtCCTAcTAA   CgctAAAAAAtTATTgGTAC
16 5762 aCTTGCAGTTGGaCATCCcTATTTTcCTATTAAAAAACCTAACAAT   AAcAAAA    TATTaGTtC
31 5678 gCTTACAGTaGGcCATCCATATTaTtCcATacctAAAtCTGACAATccTAAaAAAA    TAGTTGTaC
18 5738 atTaACtGTtGGtaATCCATATT       TtagggttcCTGcaggTggTggcAAtAagcagGaTaTtC

con     -cTtgC-GTtGGacATCCaTATTtttctaTtaaaaaacctgctaat--caacaaaAaa-tagttgTaC
          JJ27-GTTGGACATCCATATTTT-JJ27
    O27-TCTTGCTGTTGGCCATCCATATTTTTCTATTAAAAATCCTACTAA   CGCTAAAAAATTATTGGTAC-O27


 6 5967 CAAAGGTGTCaGGATATCAATAcAGgGTaTTTAAGGTgGTGTTaCCAGATCCTAACAAaTTTGCATTg
11 5949 CAAAGGTGTCtGGATATCAATATAGaGTgTTTAAGGTaGTGTTgCCAGATCCTAACAAgTTTGCATTa
33 5784 CcAAAGTATCAGGcTTgCAATATAGGGTtTTTAGGGTcCgTTTACCAGATCCTAATAAaTTTGGATTT
16 5824 CtAAAGTATCAGGATTACAATAcAGGGTATTTAGaaTaCaTTTACCtGAcCCcAATAAgTTTGGtTTT
31 5743 CaAAGGTgTCAGGATTACAATATAGGGTATTTAGGGTtCgTTTACCaGAtCCAAAcAAATTTGGaTTT
18 5800 CtAAGGTtTCtGcATacCAATATAGaGTATTTAGGGTgCagTTACCtGAcCCAAAtAAATTTGGtTTa

con     CaAAgGTgTCaGgaT--CAATAtAGgGTaTTTAgggT-c--TTaCCaGAtCCtAA-AAaTTTGgaTTt
                    JJ28-CAATATAGGGTATTTAGGGTNCNGTTACC-28 30-AATAAATTTGGATTN
                    PCR4-GTTATATCCCATAAATCCCATGTTAA-PCR4PCR5-TTATTTAAACCAAAA
    O27-CCAAAGTATCAGGCTTGCAATATAGGGTTTTTAGGGTCCGTTTACCAGATCCTAATAAATTTGGATTT-O27


 6 6035 CCTGAcTCgTCtCTtTTcGAtCCCACaACACAaCGTTTAGTATGGGCaTGCACAGGccTaGAGGTgGG
11 6017 CCTGAtTCaTCCCTgTTTGACCCCACTACACAgCGTTTAGTATGGGCgTGCACAGGgtTgGAGGTAGG
33 5852 CCTGACACCTCCTTTTATAACCCtGATACACAaCGaTTAGTATGGGCaTGTGTAGGccTTGAaaTAGG
16 5892 CCTGACACCTCaTTTTATAATCCaGATACACAgCGgcTgGTTTGGGCCTGTGTAGGTgTTGAGGTAGG
31 5811 CCTGATACaTCTTTTTATAATCCTGAAACtCAACGcTTAGTTTGGGCCTGTGTTGGTtTaGAGGTAGG
18 5868 CCTGATACtagTaTTTATAATCCTGAAACaCAACGtTTAGTgTGGGCCTGTGcTGGagTgGAaaTtGG

con     CCTGA-aC-tcttTtTataAtCCtga-ACaCAaCGttTaGTaTGGGCcTGtg-aGG--T-GAggTaGG
        CCTGACACCTCNNTTTATAAT-JJ30
        GGACTGTGGA-PCR5
    O27-CCTGACACCTCCTTTTATAACCCTGATACACAACGATTAGTATGGGCATGTGTAGGCCTTGAAATAGG-O27
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 6 6103 CAGGGGaCAgCCaTTAGGtGTgGGTGTaAGTGGaCATCCtTTcCTAAAtAAATATGATGATGTtGAAA
11 6085 CAGGGGtCAaCCtTTAGGCGTTGGTGTtAGTGGgCATCCaTTgCTAAACAAATATGATGATGTaGAAA
33 5920 TAGaGGgCAGCCATTAGGCGTTGGCATaAGTGGtCATCCTTTATTAAACAAATTTGATGACACtGAAA
16 5960 TCGtGGtCAGCCATTAGGTGTgGGCATTAGTGGcCATCCTTTATTAAATAAATTgGATGACACaGAAA
31 5879 TCGcGGgCAGCCATTAGGTGTaGGtATTAGTGGtCATCCATTATTAAATAAATTtGATGACACTGAAA
18 5936 cCGtGGtCAGCCtTTAGGTGTtGGccTTAGTGGgCATCCATTtTatAATAAATTaGATGACACTGAAA

con          --G-GGtCAgCCaTTAGGtGTtGG-aTtAGTGG-CATCC-TTattaAAtAAATttGATGAcactGAAA
        O27-TAGAGGGCAGCCATTAGGCGTTGGCATAAGTGGTCATCCTTTATTAAACAAATTTGATGACACTGAAA-O27


 6 6171 AT    tcaGGGagTGGTGGTAAcCCTGGaCAGGATAAcAGGGTTAATGTAGGTATGGATTATAAACAA
11 6153 ATaGTggtGGGTATGGTGGTAAtCCTGG.:AGGATAATAGGGTTAATGTAGGTATGGATTATAAACAA
33 5988 ccGGTAacaaGTATcCTGGAcAaCCgGGTGctGATAATAGGGAATGTtTATCcATGGATTATAAACAA
16 6028 AtGCTAgTgctTATGCaGcAaATgCaGGTGtgGATAATAGaGAATGTATATCtATGGATTAcAAACAA
31 5947 AcTCTAATagaTATGCcGgTggTcCTGGcactGATAATAGGGAATGTATATCaATGGATTATAAACAA
18 6004 gtTCccATgccgccaCgtcTaaTgtTtctgagGAcgtTAGGGAcaaTgTgTCtgTaGATTATAAgCAg

con          at-ctaatgggtatgctggtaatcctggtgagGAtaatAGgGaa--TgTatctaTgGATTAtAAaCAa
        O27-CCGGTAACAAGTATCCTGGACAACCGGGTGCTGATAATAGGGAATGTTTATCCATGGATTATAAACAA-O27


 6 6236 ACaCAatTATGcATGGTtGGaTGTGCcCCcCCtTTgGGcGAgCATTGGGGTAAaGGTAaACAgTGTaC
11 6221 ACcCAGcTATGTATGGTgGGcTGTGCtCCaCCgTTAGGtGAACATTGGGGTAAgGGTAcACAaTGTtC
33 6056 ACACAGTTATGTTTAcTTGGaTGTAAgCCtCCaAcAGGGGAACATTGGGGTAAAGGTgttgCtTGTAC
16 6096 ACACAATTGTGTTTAaTTGGTTGCAAACCACCTATAGGGGAACAcTGGGGcAAAGGatccCCaTGTAC
31 6015 ACACAAcTGTGTTTAcTTGGTTGCAAACCACCTATTGGaGAgCAtTGGGGTAAAGGtAgTCCTTGTAg
18 6072 ACACAgtTaTGTaTttTgGGcTGtgccCCtgCTATTGGgGAaCAcTGGGcTAAAGGcAcTgCTTGTAa

con          ACaCA-tTaTGt-Ta-TtGG-TGt---CCacCtataGGgGAaCAtTGGGgtAAaGGtactcctTGTac
        O27-ACACAGTTATGTTTACTTGGATGTAAGCCTCCAACAGGGGAACATTGGGGTAAAGGTGTTGCTTGTAC-O27
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 6 6304 tAATACacCTGTACAggcTGGTGACTGCCCgCCcTTaGAACTTATTACCAGTGTTATACAGGATGGcG
11 6289 aAATACctCTGTACAaaaTGGTGACTGCCCcCCgTTgGAACTTATTACCAGTGTTATACAGGATGGgG
33 6124    TAaTGCAGcACcTgCcaaTGATTGTCCACCtTTAGAACTTATAAAtACTaTTATTgAGGATGGTG
16 6164 cAATgtTGCAGTAAaTCCaGGTGATTGTCCACCATTAGAgTTAATAAAcACAGTTATTCAGGATGGTG
31 6083 tAAcaaTGCTaTtACcCCtGGTGATTGTCCtCCATTAGAATTAAAAAAttCAGTTATaCAAGATGGgG
18 6140 atcgcgTcCTtTatCaCagGGcGATTGcCCcCCtTTAGAAcTtAAAAAcaCAGTTtTggAAGATGGtG

con     -aata-tgCtgtac--cctggtGAtTG-CC-CC-TTaGAacTtAtaAacac-gTTaTacAgGATGGtG
                                                                 JJ36-GATGGTG
   O27-    TAATGCAGCACCTGCCAATGATTGTCCACCTTTAGAACTTATAAATACTATTATTGAGGATGGTG-O27
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 6 6372 AtATGGTTGAcACAGGCTTTGGTGCTATGAATTTTGCtGAtTTgCAgACCAATAAATCaGATGTTCCt
11 6357 AcATGGTTGAtACAGGCTTTGGTGCTATGAATTTTGCAGAcTTaCAaACCAATAAATCgGATGTTCCc
33 6189 ATATGGTgGAcACAGGaTTTGGTtgcATGGATTTTAaAACATTgCAGGCTAATAAAAGTGATGTTCCt
16 6232 ATATGGTTcATACtGGCTTTGGTGCTATGGAcTTTACTACATTACAGGCTAAcAAAAGTGAaGTTCCa
31 6151 ATATGGTTGATACaGGCTTTGGaGCTATGGAtTTTACTgCtTTACAAGAcACTAAAAGTaAtGTTCCt
18 6208 ATATGGTaGATACtGGaTaTGGtGCcATGGAcTTTAgTaCaTTgCAAGAtACTAAAtGTgAgGTaCCa

con     AtATGGTtgAtACaGGcTtTGGtgctATGgAtTTTact-caTT-CA-gc-AatAAA-gtgAtGTtCCt
        ATATGGTTGATACAGGCTTTGGTGCTATGGA-36   37-CATTNCANGCNAATAAANGTGATGTTCCT
    O27-ATATGGTGGACACAGGATTTGGTTGCATGGATTTTAAAACATTGCAGGCTAATAAAAGTGATGTTCCT-O27
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 6 6440 aTTGAcATaTGTGGcACTacaTGtAAATATCCaGATTATTTaCAAATGGCTGCAGACCCaTATGGTGA
11 6425 cTTGATATTTGTGGaACTgtcTGCAAATATCCtGATTATTTgCAAATGGCTGCAGACCCTTATGGTGA
33 6257 aTTGATATTTGTGGcAgTAcaTGCAAATATCCAGATTATTTaAAAATGaCTagtGAgCCTTATGGTGA
16 6300 cTGGATATTTGTAcaTCTATTTGCAAATATCCAGATTATaTTAAAATGGTgtCaGAaCCATATGGCGA
31 6219 TTGGAcATTTGTAAtTCTATTTGTAAATATCCAGATTATcTTAAAATGGTTGCtGAgCCATATGGCGA
18 6276 TTGGAtATTTGTcAgTCTATTTGTAAATATCCtGATTATtTacAAATGtcTGCaGAtCCtTATGGgGA

con     -T-GAtATtTGTgg--cTattTG-AAATATCCaGATTATtTa-AAATGgctgcaGA-CC-TATGGtGA
        NTNGATATTTGT-JJ37  JJ38-AAATATCCAGATTATTTANAAATGG-JJ38
    O27-ATTGATATTTGTGGCAGTACATGCAAATATCCAGATTATTTAAAAATGACTAGTGAGCCTTATGGTGA-O27
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 6 6508 TAGaTTaTTTTTTTtTcTaCGgAAGGAACAAATGTTTGCcAGACAtTTTTTTAAcAGGGCtGGcgagG
11 6493 TAGgTTgTTTTTTTaTtTgCGAAAGGAACAAATGTTTGCtAGACACTTTTTTAATAGGGCcGGTACtG
33 6325 TAGtTTATTTTTcTtTcTtCGAcGtGAACAAATGTTTGTaAGACACTTTTTTAATAGGGCTGGTACat
16 6368 cAGcTTATTTTTTTATTTACGAAGGGAACAAATGTTTGTtAGACATTTaTTTAATAGGGCTGGTACtG
31 6287 TACaTTATTTTTTTATTTACGtAGGGAACAAATGTTTGTaAGGCATTTTTTTAATAGAtCAGGcACgG
18 6344 TtCcaTgTTTTTTTgcTTACGgcGtGAgCAgcTtTTTGctAGGCATTTTTggAATAGAgCAGGtACta

con     tag-tTaTTTTTtTattTaCGaaggGAaCAaaTgTTTG-tAGaCAtTTtTttAAtAGggCtGGtactg
                                                                WO 86/05816-GAGG
    O27-TAGTTTATTTTTCTTTCTTCGACGTGAACAAATGTTTGTAAGACACTTTTTTAATAGGGCTGGTACAT-O27

 6 6576 TGGGGGAACCTGTGCCTGATacaCTtaTaaTtAAgGGtaGTggaAAtcGcaCgTCTGTAGggAGTAGT
11 6561 TGGGGGAACCTGTGCCTGATGACCTGTTggTaAAAGGggGTaatAAcAGatCaTCTGTAGctAGTAGT
33 6393 TaGGaGAggCTGTtCCcGATGACCTGTACATTAAAGGtTCaGGaACTACTGCcTCTaTtcaaAGcAGT
16 6436 TTGGTGAAaaTGTaCCaGAcGAtTTATACATTAAAGGCTCtGGgTCTACTGCaAaTTTAGCcAGttca
31 6355 TTGGTGAAtCgGTcCCTactGACTTATATATTAAAGGCTCcGGTTCaACaGCTACTTTAGCtAaCaGT
18 6412 TgGGTGAcaCtGTgCCTcaatcCTTATATATTAAAGGCaCaGGTatgcCtGCTtCacctGgcAgCtGT

con     TgGGtGAa-ctGTgCCtgatgac-Tata-aTtAAaGGctctggtactactgC-tct-tagc-Ag-agt
        TGGGGGAACCTGTGCCTGATACACTTATAATTAAGGGTAGTGGAAATCGCACGTCTGTA-WO86/05816
                         LCR2A-ACCTGTTGGTAAAAGGGGGTAATAA-LCR2A
                         LCR2A'-GGACAACCATTTTCCCCCATTATT-LCR2A'
                                                  LCR2B-CAGATCATCTGTAGCTAGTAGT
                                                 LCR2B'-GTCTAGTAGACATCGATCATCA
                         LCR3A-ATTTATACATTAAAGGCTCTGGGTC-LCR3A
                         LCR3A'-AAATATGTAATTTCCGAGACCCAG-LCR3A'
                                                  LCR3B-TACTGCAAATTTAGCCAGTTCA
                                                 LCR3B'-ATGACGTTTAAATCGGTCAAGT
                         LCR4A-CCTTATATATTAAAGGCACAGGTAT-LCR4A
                         LCR4A'-GAATATATAATTTCCGTGTCCATA-LCR4A'
                                                  LCR4B-GCCTGCTTCACCTGGCAGCTGT
                                                 LCR4B'-CGGACGAAGTGGACCGTCGACA
    O27-TAGGAGAGGCTGTTCCCGATGACCTGTACATTAAAGGTTCAGGAACTACTGCCTCTATTCAAAGCAGT-O27
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 6 6644 ATaTATGTtaAcACcCCgAGcGGCTCtTTGGTGTCcTCtGAGGCaCAATTgTTTAATAAgCCATATTG
11 6629 ATTTATGTaCAtACaCCTAGTGGCTCATTGGTGTCTTCaGAGGCTCAATTATTTAATAAaCCATATTG
33 6461 gcTTtTTTTCCcACtCCTAGTGGaTCAATGGTTACTTCcGAatCTCAgTTATTTAATAAgCCATATTG
16 6504 AaTTATTTTCCTACACCTAGTGGtTCtATGGTTACcTCtGATGCcCAAATATTcAATAAACCtTATTG
31 6423 AcaTAcTTTCCTACACCTAGcGGCTCcATGGTTACtTCaGATGCaCAAATtTTTAATAAACCATATTG
18 6480 gtgTAtTcTCCctCtCCaAGtGGCTCtATtGTTACcTCtGActCcCAgtTgTTTAATAAACCATATTG
con     attTatttcc-aCaCCtAGtGGcTCtaTgGTtaC-TCtGA-gC-CAatTaTTtAATAAaCCaTATTG
        AT-LCR2B                      JJ39-GTTACNTCTGANGCNCAATTATTTAATAAACCATATTG
        TAA-LCR2B'
        AA-LCR3B
        TTA-LCR3B'
        GT-LCR4B
        CAC-LCR4B'
    O27-GCTTTTTTTCCCACTCCTAGTGGATCAATGGTTACTTCCGAATCTCAGTTATTTAATAAGCCATATTG-O27

 6 6712 GCTaCAAAAaGCcCAGGGACATAACAATGGTATTTGtTGGGGtAAtCAacTGTTTGTTACTGTGGTAG
11 6697 GCTtCAAAAgGCtCAGGGACATAACAATGGTATTTGcTGGGGaAAcCActTGTTTGTTACTGTGGTAG
33 6529 GCTACAACGtGCACAaGGtCATAATAATGGTATTTGTTGGGGcAAtCAggTATTTGTTACTGTGGTAG
16 6572 GtTACAACGaGCACAGGGcCACAATAATGGcATTTGTTGGGGtAAcCAacTATTTGTTACTGTtGTtG
31 6491 GaTgCAACGtGCtCAGGGaCACAATAATGGTATTTGTTGGGGcAATCAgTTATTTGTTACTGTGGTAG
18 6548 GtTaCAtaagGCaCAGGGtCAtAAcAATGGTgTTTGcTGGcatAATCAaTTATTTGTTACTGTGGTAG

con     GcTaCAa---GCaCAgGGaCAtAA-AATGGtaTTTGtTGGggtAAtCAatTaTTTGTTACTGTgGTaG
        GCTACAANNNGCACA-JJ39 J41-AATGGTATTTGTTGGGGTAATCAATTATTTGTTACTGTGGTAG
               C6-GCMCAGGGWCATAAYAATGG-C6                         C1-CTGTGGTAG
                                                                  C7-CTGTTGTTG
                                                                  C8-CTGTGGTAG
                                                                 C10-CAGTTGTAG
                                                                 C11-CTGTGGTTG
                                                                 C12-CTGTTGTGG
                                                                 C13-CTGTTGTAG
                                                                 C14-CTGTGGTAG
                                                                 C15-CTGTAGTGG
    O27-GCTACAACGTGCACAAGGTCATAATAATGGTATTTGTTGGGGCAATCAGGTATTTGTTACTGTGGTAG-O27
```

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 6 6780 ATACCACACGCAGTACcAAcATGACAtTATG       TGCATCcGTaaCTAcATCTtCcACATACACc
        |||||||||||||||| || |||||| ||||       |||||| ||  ||| |||| | ||||||||
11 6765 ATACCACACGCAGTACaAATATGACAcTATG       TGCATCtGTgtCTAaATCTgCTACATACACt
        ||||||| |||||||| ||||||||  ||||         ||   ||  |||       |||||| |
33 6597 ATACCACtCGCAGTACtAATATGACtTTATG       caCAcaAGTaACTAgtGAcAgTACATATAAA
        |||| || |||||||| |||||| | |||||         |   |   |||   || | ||||||||||
16 6640 ATACtACACGCAGTACaAATATGTCaTTATGTGCT    GCcATAtCtACTtcaGAaACTACATATAAA
        |||| ||||| ||||| ||||||||  | ||||||    || ||  | |     || ||||||| ||||
31 6559 ATACCACACGtAGTACCAATATGTCtgTtTGTGCT    GCAATtgCaAacagtGATACTACATtTAAA
        ||||||| |  ||||||||| |  |  | ||||||     ||    |         |     || | |
18 6616 ATACCACtCccAGTACCAATtTaaCaaTaTGTGCTTctaCAcagtCtcctgtaccTgggcaATaTgAt
con     ATACcACaCgcAGTACcAAtaTgaCatTaTGtgct--tgCa---g-aacta-ag-tactacATataaa
        ATACC-JJ41                         C16-CATCCGTAACTACATCTTCCA-C16
        ATACCACACGCAGTAC-C1                    C17-TCTGTGTCTAAATCTGCTACA-C17
        ATACTACACGCAGTAC-C7                C20-CACACAAGTAACTAGTGACAG-C20
        ATACCACTCGCAGTAC-C8                    C23-CAGTCTCCTGTACCTGGG-C23
        ATACTACTCGCAGCAC-C10                    C31-TTGCAAACAGTGATACTACATT-C31
        ATACTACCCGTAGTAC-C11
        ATACTACCAGAAGCAC-C12
        ATACTACTAGAAGCAC-C13
        ATACCACACGTAGTAC-C14
        ACACTACCCGCAGTAC-C15
    O27-ATACCACTCGCAGTACTAATATGACTTTATG       CACACAAGTAACTAGTGACAGTACATATAAA-O27

 6 6842 AATTCtGATTATAAaGAgTACATGCGtCATGTGGAaGAGTaTGATTTACAaTTTATTTTTCAATTaTG
        ||||| |||||||| || |||||||| |||||||| |||| ||||||||| |||||||||||||| ||
11 6827 AATTCAGATTATAAgGAATACATGCGcCATGTGGAgGAGTtTGATTTACAGTTTATTTTTCAATTgTG
        |||  | ||| ||| ||||| ||  | ||||| || || | |||| |||||||| |||||||| | ||
33 6659 AATgaAAATTTTAAaGAATAtATAaGACATGTtGAaGAATATGATcTACAGTTTgTTTTTCAACTaTG
        |||   || ||||| || ||  || ||||||  || ||||||||| |||||||| |||||||||| ||
16 6705 AATAcTAAcTTTAAgGAGTAccTAcGACATGGgGAGGAATATGATTTACAGTTTATTTTTCAACTgTG
        | || ||| ||||| |||||  || ||||||| ||||||| ||||||||| ||||| |||||  | ||
31 6624 AgTAgTAAtTTTAAaGAGTATtTAAGACATGGTGAGGAATtTGATTTACAaTTTATaTTTCAGTTaTG
          ||  || |||||  |||||   ||||||| |||||||| |||||| || ||||| |||||||| ||
18 6684 gcTAccAAaTTTAAgcAGTATagcAGACATGtTGAGGAATaTGATTTgCAgTTTATtTTTCAGTTgTG

con     aaTactaAtTtTAA-gAgTA-ata-GaCATGt-GAgGAaTaTGATtTaCAgTTTaTtTTTCAatT-TG
    O27-AATGAAAATTTAAAGAATATATAAGACATGTTGAAGAATATGATCTACAGTTTGTTTTTCAACTATG-O27

 6 6910 TAGCATTACATTgTCTGCtGAAGTaATGGCCTATATtCACACAATGAATCCcTCTGTTTTGGAaGACT
        |||||||||||| ||||| ||||| ||||||||||| |||||||||||||| ||||||||||| ||||
11 6895 TAGCATTACATTATCTGCAGAAGTcATGGCCTATATaCACACAATGAATCCtTCTGTTTTGGAgGACT
         |   |||| ||| |||||||||| ||| | ||||| ||  | ||||||||   | |||| || || |
33 6727 CAAAgTTACCTTAACTGCAGAAGTTATGACATATATtCATgCTATGAATCCagaTATTTTaGAaGAtT
        |||| | |||||||||||||| ||||||||||| || ||| |||||||| |   |||||| || || |
16 6773 CAAAATAACCTTAACTGCAGACGTTATGACATAcATaCATtCTATGAATtCcaCTATTTTGGAgGAcT
        ||||||||| ||| |||||||| | |||||||| || ||   ||||||| |  |||||||||| || |
31 6692 CAAAATAACaTTAtCTGCAGACaTaATGACATATATTCAcAGTATGAATcCtgCTATTTTGGAaGATT
         |  || || ||| |||||||  | ||| | |||||||| |||||||||     |||||| || ||||
18 6752 tActATtACtTTAaCTGCAGAtgTtATGtCcTATATTCAtAGTATGAATagcagTATTTTaGAgGATT

con     -AaaaTtACaTTa-CTGCaGAagTtATGaC-TAtATtCA-actATGAATccc-cTaTTTTgGA-GA-T
    O27-CAAAGTTACCTTAACTGCAG-O27
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  6 6978 GGAACTTTGGgTTATCGCCTCCcCCAAATGGTACAtTaGAaGATACcTATAGgTATGTgCAGTCACAG
         |||||||||| ||||||||||| |||||||||||| | || ||||| ||||| ||||| |||||||||
 11 6963 GGAACTTTGGTTTATCGCCTCCaCCAAATGGTACAcTgGAGGATACtTATAGaTATGTaCAGTCACAG
         || | ||||||||| | ||||| |||  || ||   |  ||||||| ||||| | |||    || |||
 33 6795 GGcAaTTTGGTTTAaCACCTCCtCCAtcTGcTAgttTAcAGGATACcTATAGGTTTGTtaccTCtCAG
         || | |||||| ||  |||||| |||   |  |   || | ||||| |||||||||||     | |||
 16 6841 GGAATTTTGGTcTAcaACCTCCcCCAggAGGcACacTAGAaGATACtTATAGGTTTGT   aaCcCAG
         ||||||||||  |     | || ||   |||  |  | || ||||| |||||||||||     | |||
 31 6760 GGAATTTTGGatTgaCCaCaCCtCCctCAGGTtCTTTGGAGGATACcTATAGGTTTGTcaccTCaCAG
         |||| |||||  |  || | || ||  |   |  ||||| |||||| ||| | |||||    ||
 18 6820 GGAAcTTTGGtgTtcCCcCcCCcCCaaCtacTagTTTGGtGGATACaTATcGtTTTGTacaaTCtgtt
con      GGaAcTTTGGttTa-c-cCtCCcCCaactggtac-tT-gagGATACcTATaGgTtTGTaca-tCacag
                                                           C21-TTGT   AACCCAG
                                                          C34-TTTGT   AACCCAG
                                                         C35-GTTTGT   AACCCAG

  6 7046 GCCATTACCTGTCAaAAgCCCACtCCTGAAAAgGAAAAgCcaGA    TCCCTATAAGaAccTtAGTT
         |||||||||||||| || ||||| |||||||| ||||| |  ||    |||||||||| |  | ||||
 11 7031 GCCATTACCTGTCAgAAACCCACACCTGAAAAaGAAAAaCAgGA    TCCCTATAAGgAtaTgAGTT
         || ||||| ||||| ||| |   ||||  ||| |||||  | ||     ||||      |    |  |
 33 6863 GCtATTACgTGTCAAAAAaCagtACCTCCAAAgGAAAAgGAAGA    CCCCTTAggtAAATAtACaT
         || ||| | |||||||||     |||||||      || |||||    |||||||   ||||| || |
 16 6906 GCaATTgCtTGTCAAAAAcaTaCACCTCCAgcaCCtAAaGAAGATgatCCCCTTA AAAAATAcACtT
         || ||| | |||||||||  | | || | |   || || ||||||   ||  ||| || | ||   ~|
 31 6828 GCcATTACaTGTCAAAAAacTGCcCCcCaAaagCCcAAgGAAGAT   CCaTTTA AAgAtTAtgtaT
         || ||||| ||||||||   |||  | |        ||  | |||   || | |  |  | |     |
 18 6888 GCtATTACcTGTCAAAAggaTGCtgCaCcggctgaaAAtaAgGAT   CCcTaT gAtaAgTtaaagT

con      GCcATTaCcTGTCAaAAacct-cacCtc-aaaggaaAAggaaGAt---cCccttaaa-aA-t-ta-tT
         GCAATTGCT-C21 C18-CATACACCTCCAGCACCTAA-C18                    JJ46-T
                      C19-GGATGCTGCACCGGCTGA-C19
                   C22-AAAAACAGTACCTCCAAAGGA-C22
                   C27-TTTTTGTCATGGAGGTTTCCT-C27
                         C24-CACACCTGAAAAAGAAAAACAG-C24
                         C28-GTGTGGACTTTTTCTTTTTGTC-C28
                           C25-CTCCTGAAAAGGAAAAGCCA-C25
                           C26-GAGGACTTTTCCTTTTCGGT-C26
                               C29-CCAAAAGCCCAAGGAAGAT       C-C29
                                C30-CAAAAGCCCAAGGAAGAT       C-C30
                 C32-CAGAAACCCACACCTGAAAAAGA-C32
                  C33-AGAAACCCACACCTGAAAAAGAA-C33
         GCAATTGCT-C34                        O23-GGA    TCCCTATAAGGATATGAGTT
         GCAATTGCT-C35                        O15-GGAT   CCCTAT GATAAGTTAAAGT
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 6 7110 TTTGGGAGGTTAAtTTAAAAGAAAAGTTTTCtAGTGAATTgGATCAGTaTCCttTgGGACGcAAGTTT
        ||||||||||||| |||||||||||||||||| |||||||| ||||||| |||   | ||||| ||||||
11 7095 TTTGGGAGGTTAAcTTAAAAGAAAAGTTTTCAAGTGAATTAGATCAGTTTCCccTtGGACGtAAGTTT
        ||||||| ||  | ||||| ||||| ||||||    || ||||||||||||||   | ||||| ||||||
33 6927 TTTGGGAAGTggATTTAAAGGAAAAaTTTTCAGCAGAtTTAGATCAGTTTCCTTTgGGACGCAAGTTT
        ||||||||||   |||||||||||||| ||||| |||||  ||||||||||||||||| |||||||| |||
16 6973 TTTGGGAAGTaAATTTAAAGGAAAAGTTTTCTGCAGAccTAGATCAGTTTCCTTTaGGACGCAAATTT
        ||||||| || ||||||||| ||||||||||||||||  |||||||||||||| | || |||||||||
31 6892 TTTGGGAgGTtAATTTAAAaGAAAAGTTTTCTGCAGAtTTAGATCAGTTTCCaCTgGGtCGCAAATTT
        ||||| | ||  ||||||| ||||||||||||  ||| |||||||| | ||| || || || ||||||
18 6952 TTTGGaAtGTggATTTAAAgGAAAAGTTTTCTttAGAcTTAGATCAaTaTCCcCTtGGaCGtAAATTT

con     TTTGGgAgGTtaAtTTAAA-GAAAAgTTTTCtgcaGA-tTaGATCAgTtTCCt-TgGGaCGcAA-TTT
        TTTGGGAGGTTAATTTAAANGAAAAGTTTTCTGCAGANTTAGATCA-JJ46
                                            C2-GATCAGTTTCCYYTKGGACG-C2
                                            C3-GATCAGTWTCCYYTKGGACG-C3
                                            C7-CTAGTCAWAGGRRAMCCTGC-C7
    O15-TTTGGAATGTGGATTTAAAGGAAAAGTTTTCTTTAGACTTAGATCAATATCCCCTTGGACGTAAATTT-O15
    O23-TTTGGGAGGTTAACTTAAAAGAAAAGTTTTCAAGTGAATTAGATCAGTTTCCCCTTGGACGTAAGTTT-O23


 6 7178 TT    gTT                                          aCAAAGTGGATATaGgGGACGGtCcT
        ||     ||                                           |||||||||||| | |||||| | |
11 7163 TTA    TT                                          gCAAAGTGGATATcGAGGACGGaCgT
        |||    ||                                           |     |       |
33 6995 TTA    TTAcagGcAggtcttaaagcAaaAcctaaacttaaACGtgcAGcccccaCAtCcaCCcgCA
        |||       |   | |           |  |         | |  |       |  |  ||  ||
16 7041 TTA cTACAAGCAGGATtgAaGGCcaaACCAAAATTTAcAttAGGaAAACGaaaagCTaCACCCacCA
        |||  |||| ||||||| | |||    || ||||||| |  ||| |||||       | |||||
31 6960 TTA tTACAGGCAGGATatAGGGCacgtCCtAAATTTAaAgCAGGtAAACG   TagTgCACCC   t
        ||   | ||||| ||||   |        || |   |    |  | |||||    |
18 7020 TT ggTtCAGGCtGGATtgcGtcgcaagCCcAccaTaggccCtcGcAAACG   T          tctg

con     TTa--ta--agcaggattgagggcaaaaccaaaaataa-a-cacgaaaa-gatatag-gcaccc-cct
    O15-TT GGTTCAGGCTGGATTGCGTCGCAAGCCCACCATAGGCCCTCGCAAACG   T          TCTG-O15
    O23-TTA    TT                                          GCAAAGTGGATATCGAGGACGGACGT-O23


 6 7209 CTatTCGTACAGGTgTtAAGCGCCCtGCTGTtTCcAAagCCTCTgCtGCCCCtAAACGtAAgCGcgCC
        ||  |||||||||| | ||||||||| ||||| || ||  ||||| | ||||| ||||| || ||  ||
11 7194 CTgCTCGTACAGGTaTaAAGCGCCCaGCTGTgTCtAAgcCCTCTaCAGCCCCcAAACGaAAaCGTaCC
        |  |    | ||      ||                 |   |      |      |      |
33 7059 CaTCgTCTgCAaaacgcAAaaaggttaaaaAATAAcAcTttGtgtaAttgtgtTAtgtTGTtgtTttg
        | || ||| |        |             || ||   |  |    |      |   |||
16 7108 CcTCATCTACCtCTACAACtGCtAAACG cAAAAAACgTAAGctGTAA  GtaTTGTATGTA
        |  ||||||||| |||||| | || |||||  ||||||| |||    ||||  |   ||||||||
31 7021 CagCATCTACCACTACAcCaGCaAAACGtaAAAAAAC TAAAaaGTAAtgGatgTGTATGTAAtaCaT
        |  ||||| |||||||                  | ||||                 ||  |  | |
18 7075 CtcCATCTgCCACTAC                gtcttC TAAA              ccTGccAagCgT

con     Ct-catcTaC-actacaaa---c--a--t-aat-aa-gtaa-ctg-a-cc-ct-a-c-tgta--tcc-
    O15-CTCCATCTGCCACTAC                GTCTTC TAAA              CCTGCCAAGCGT-O15
    O23-CTGCTCGTACAGGTATAAAGCGCCCAGCTGTGTCTAAGCCCTCTACAGCCCCCAAACGAAAACGTACC-O23
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 6 7277 AAAACtAAAAgGTAATATATGTGT    aTaTGTacTGTT
        ||||| |||| |||||||||||||     | |||  ||||
11 7262 AAAACcAAAAaGTAATATATGTGTgtcagTGTGTTGTGTT
                |      |     |||     |||||||||||
33 7127 TtcTGtcTAtGTactTtgtgTTGT     TGTGTTGTGTTgtTGT
        |  ||  |  ||        ||||     |||||        |||
16 7167 TgtTGaaTtaGTGT   TGtTTGT     TGTGT     ATATGT
           |   |  ||||   || ||||       |||     ||||||
31 7088 GTGTctgTatGTGTAtGTGCTTGTgctgtatTGT     ATATGTGTGTGTttgtgtgtTATATA tg
        |||       ||||| ||||            |      ||||||||||||        ||||||
18 7113 GTG      cGTGTAcGTGC          caGgaagtaATATGTGTGTGT gtatataTATATAcat

con     -t-tctataagtgtat-tgtttgtg----tgtGtagtgt-tatgtgtgtgt--------tatata---
    O15-GTG      CGTGTACGTGC          CAGGAAGTAATATGTGTGTGT GTATATATATATACAT-O15
    O23-AAAACCAAAAAGTAATATATGTGTGTCAGTGTGTTGTGTT-(O23)


 6 7313             AT
                    ||
11 7302             ATtTaTATG         T                TGTTGTA     gTGTGT
                     | | ||||         |                |||||||      |||||
33 7167     TTGT TtTtTgTGTATG         TGttacaaTgtATgTTATGTTGTATGTtacTGTGTTTG
            |||| | |   ||||||         ||      |  || ||| |||||||||    |||||||
16 7199     TTGTATGTgctTGTATG         TG  CTTGTAaATATTAaGTTGTATGT    GTGTTTG
             |||||||   ||||||             |||||| ||||    | ||||||     ||| ||
31 7150 gTATaTGTATGTTTaTGTATG CgTGTGT    aCTTGTATATAT GtaTaGTATGT   TATGTgTG
         |||   | |||||  ||||| | |||||      |||| | ||| |     |       ||||   |
18 7164 cTATtgtTgTGTTT  GTATGtCcTGTGTtgtgtTTGT  TgTAT G    aTtgcattgTATG   G

con     -tatttgtatgtttttgtatg-c-tgtgt-tgt-cttgtatatattatgttgtatgtt-gtgtgtttg
    O15-CTATTGTTGTGTTT  GTATGTCCTGTGTTTGTGTTTGT  TGTAT G    ATTGCATTGTATG   G-O15
    O23-            ATTTATATG         T                TGTTGTA     GTGTGT(-O23)


 6 7315                                                       aTATATGT
                                                               |||||||
11 7325                              aTATGT TtCTTGT atTGTG     TATATGT
                                      ||||| | |||||   ||||     | |||||
33 7221 T                           ttTATGTgTaCTTGTttGTGTGcATGTTcTATGTacttgt
        |                                            ||||| ||||
16 7248 TATGTATG       gtaTAATAAA                 cacGTGTGTATGT
        ||||||||          |||||||                     |||||||||
31 7209 TATGTATGctatgtaTGTTAATAAAtatgtgtatacctgtgtgtgtTGTGTATGTTGTcctTataTAc
        ||||||||       ||||                             ||||||||||   |   ||
18 7221 TATGTATG     gtTGTT                           gtTGTATGTTGTatgTtacTAt

con     tatgtatg-------tgttaataaa----ttatgt-ttcttgtt-gtgtgtatgtt-tatgta--tat
    O15-TATGTATG     GTTGTT                           GTTGTATGTTGTATGTTACTAT-O15
    O23-                             ATATGT TTCTTGT ATTGTG     TATATGT(-O23)
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 6 7323    GT                                                    gTATGTAcTGT
              ||                                                     |||||| |||
11 7351    GTataTGTTTGTGTATATGT                GTAT             gtTATGTA TGT
               |   |||||||||||||||                ||||               |||||| |||
33 7262 cagtTtccTGTTTGTGTATATGTtaataaaacattgTgTGTATtTgtTaaActATttgTATGTA TGT
                       || | |               | |     |  |  |  ||   ||       |
16 7279                GTtTtTaAaTgcTTgtgtAACTATTGT gTcATgcAacATaAaTAaacttatT
                          | | | |  ||    |||||||||    |         | |
31 7277 AccctaTtagtaacatacTaTtAcTAtTTtataAACTATTGTtccTActTgtTcctAcTtgttCCTgc
        |     |           |   |  |  |            |   |   |  |     |    |||
18 7257 AtttgtTggtatgtggcaTtaaAtaAaaTatgttttgtggtTctgTgtgTtaTgtggtTgcgcCCTag

con     a---tat-tgtttgtgtatat-ataatataagaaactatgtttttatgtaatatt--Tatgtactgt
    O15-ATTTGTTGGTATGTGGCATTAAATAAAATATGTTTTGTGGTTCTGTGTGTTATGTGGTTGCGCCCTAG-O15
    O23-   GTATATGTTTGTGTATATGT                GTAT             GTTATGTA TGT-O23

 6 7336 TATGT  aTATGT  GTgTGTGTTctGTGTGTaatgtaAgtTATTTGTGtAATGTGTATGTgTGTT
        |||||   |||||  || ||||||||  ||||||      |  |||||||| ||||||||||| ||||
11 7386 TATGTtgtTATGTatGTtTGTGTTtaGTGTGT      gtATaTATTTGTGGAATGTGTATGTATGTT
        |||||                    |   || ||       | ||||  | |        || ||
33 7329 TATGT       AtatgggtgtaccTataTGaGTAagGagTTgTATTgcTtGccctacCcTGCATTgc
          |         |            |   |    |  |  |   |    |        | | |  |
16 7331 gtTTCaacAcctACtaaTtgTgtTgTggtTaTtcAtTGTATaTaAactaTatTtGctACATcCtgTtt
           ||   |    |   |  |  | |     |  | | ||  |         | |  | |
31 7345 TccTCccaAtagtCATgTacTTaTtTctgccTatAaTTTAggTgTcacgccaTaGTaAaAgTtgtaca
        |       |     || |   | | |          ||      |          |     |
18 7325 TgagtaacAactgtATtTgtgTtTgTggtatgggtgTTgcttgtTgggctatataTtgtccTgtattt

con     tatgtaa-aa-gt-atttgt-tttT-tgtgtgtaatgtattttatttgt-taa-ttgtatgt-tttt
    O15-TGAGTAACAACTGTATTTGTGTTTGTGGTATGGGTGTTGCTTGTTGGGCTATATATTGTCCTGTATTT-O15
    O23-TATGTTGTTATGTATGTTTGTGTTTAGTGTGT      GTATATATTTGTGGAATGTGTATGTATGTT-O23

 6 7400 TaTGTGCAATAAACAATTAcctcTtgtTacacCCTGT  gACtCAGTGgctgttgcacgcGTTtTGgT
        | |||||||||||||||||    |   |    |||||   || |||||            ||| || |
11 7450 TtTGTGCAATAAACAATTA   TTatgTgtgtCCTGTTACACcCAGTG       actaaGTTgTGtT
          ||| |        |||    |    |         ||||      |             ||
33 7390 aaTGTaCcTAccTttATTtcccTaTAtTtgtAGtaCCTACATGTttaGTattgCtttacCtTTTGaca
            |   ||  |    |    | ||     ||  ||    |||    |    |     |  |||
16 7399 ttgtTTtaTATaTactaTAtTtTgTAgcgcCAGgcCCatTTTGTaGCtTCaAcCgaAttCggTTGcat
             |    | |     | |         |        |||   ||  | |    |      |
31 7413 CccGgTccgtTtTTgcaACTaaAgctacTCCATTTTgaTTTtatGCagCCAtTTTAaaTcccTAACC
        |  | |       |    ||   |     ||||||||    |        |  |||   |    ||||
18 7393 CaaGtTataaaacTgcacACcttAcagcaTCCATTTTatccTacaatcctCcaTTTgcTgtgcAACC

con     tatgttcaa-aatt-attaccttata-t-tcc-tt-t-acat-cagtg-c-atttta--cgttt-act
    O15-CAAGTTATAAAACTGCACACCTTACAGCATCCATTTTATCCTACAATCCTCCATTTTGCTGTGCAACC-O15
    O23-TTTGTGCAATAAACAATTA   TTATGTGTGTCCTGTTACACCCAGTG       ACTAAGTTGTGTT-O23
                                                          O24-GAATTCGGTTGCAT
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 6 7466 TTGCACGCGCCtTacacacataagTaATATacaTgcAcaATATATATaTtTtgtTtaaaATACTAT
        ||||||||||| |           | ||||   |  |  |||||||| | |    |    ||||||
11 7508 TTGCACGCGCCgTtTgtgttgccTTCATAT   TatAtTATATATATtTgTaataTacCTATACTATg
        |   |    || | |         ||| |   |    |   ||    | |    |  ||   |
33 7458 TacTAgTGtCCaTATtgtacaaTTTCcTccattTTgTATGcCTAaccgTtTtcggTtACTTgCCAtac
           |  || |   |        |||       || |||| |          | |    | |  | | |
16 7467 GcTTTtTGgCaCAAaaTgTgttTTTttaAaTAgTTCTATGtCagcaacTaTGgTtTaAacTTGTAcGT
        | |||  |   ||   | |     |   | ||   |||||             | | |    || |  ||
31 7481 GtTTTCGGTTGCAttgTtTaaacaTgctAgTAcaaCTATGctgatgcagtaGTTcTGcggTTtTTgGT
        | ||||||||||                                        || ||    |  |  |
18 7461 GaTTTCGGTTGC                             ctttggcTTaTGtctgTggTttT

con     -ttt-cgg-ccctat-t-ta-a-ttc-tataa-t-ctatgt-tatat-ttt-tt-T-actttgct-tt
    O15-GATTTCGGTTGC                             CTTTGGCTTATGTCTGTGGTTTT-O15
    O23-TTGCACGCGCCGTTTGTGTTGCCTTCATAT   TATATTATATATATTTGTAATATACCTATACTATG-O23
    O24-GCTTTTTGGCACAAAATGTGTTTTTTTAAATAGTTCTATGTCAGCAACTATGGTTTAAACTTGTACGT-O24

 6 7533     aCttttatAtTTGCAACCGTTTTCGGTTGCCCTTAgCATACACTTtCCaCcAATTTGTTAcAAC
                |     | |||||||||||||||||||||||||| ||||||||| || | ||||||||| |||
11 7573 tTACCCcccccCAcTTGCAACCGTTTTCGGTTGCCCTTA CATACACTTaCCTCaAATTTGTTAtAAC
         |||||    || | |||        ||              |  |  | ||||     |   |  |
33 7526 aTACCCtaTgaCAtTGGCAGaacAgTTaaTccTTTtCTttCCTGCACTGtgtTtgTcTgTACTtgctg
         | |    |  |  ||   |   | |   |  ||| ||  |||||||||         |    ||
16 7535 TTCCTG cTtgCcaTGcgtGccaAaTcccTgtTTTcCTgaCCTGCACTG    cTTgccaACcaTtcc
        ||||||                                     |          ||       |
31 7549 TTCCTG                            aaTAcTagTTTttGCcaacaTTCTggcTtgTagt
         | |                                 || |  |||  ||     | ||   |  |
18 7496 cTgCacaatacagtacgctggcactattgcaaactttTAaTctTTTggGCactgcTcCTacaTatTttg

con     tt-c-ct-tt-catt-gcagcc--tttcg-tt-ctcttatc-T-cact--c-tcttct-tattata-c
    O15-CTGCACAATACAGTACGCTGGCACTATTGCAAACTTTAATCTTTTGGGCACTGCTCCTACATATTTTG-O15
    O23-TTACCCCCCCCCACTTGCAACCGTTTTCGGTTGCCCTTA CATACACTTACCTCAAATTTGTTATAAC-O23
    O24-TTCCTG CTTGCCATGCGTGCCAAATCCCTGTTTTCCTGACCTGCACTG    CTTGCCAACCATTCC-O24

 6 7597 GTGTTTccTctTAATCCtATATattTTGTG   CcAGGTACAcATTGCCCTGCCAAGTtgCTTGCCAA
        ||||||  |  |||||| ||||    |||||   | ||||||| |||||||||||||||  ||||||||
11 7640 GTGTTTtgTACTAATCCcATAT  gTTGTGtgcCAAGGTACAtATTGCCCTGCCAAGTatCTTGCCAA
           |     |||  | || ||     | |     ||    |     || |  | |         |
33 7594 caTTggcaTACatAcCCtATgacatTgGCagaaCAgTtAATcctTTtCTTTcCTgcacTgtgTTtgtc
          |     |         |  |        |     | | | |    |   ||   |    |    |
16 7598 aTTgTtttTtACACtgCacTatgtgcaACtActgAaTCAcTaTgTaCATTgtgTCataTAAaaTaaaT
         |  |   | ||||  |           |  |   | ||     | | || |    |    ||     |
31 7589 tTCcTgccTaACACacCTTgccaaCATATAAtccAgTCCaacTtTGCAATTAtaCtATgAAtCatgtT
          |         | |  |||     |||||||      |     ||  ||||    ||    |
18 7564 aaCaattggcgCgCctCTTtggcgCATATAA     ggCgcaccTGgtATTA gtcATtttcCtgtcc

con     -t-ttt--ta-ca-tcCtatat---tt-taa-ccaa-g-aca--Ttgc-tt-c--aatt--ttt--a-
    O15-AACAATTGGCGCGCCTCTTTGGCGCATATAA     GGCGCACCTGGTATTA GTCATTTTCCTGTCC-O15
    O23-GTGTTTTGTACTAATCCCATAT  G-O23
    O24-ATTGTTTTTACACTGCACTATGTGCAACTACTGAATCACTATGTACATTGTGTCATATAAAATAAAT-O24
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 6 7662 gtgcatcatatcctgccaaCcACACACCTGGCgcCAGGGtGCGGTATTGC     cTtactcATAA
11 7706                   CAACACACCTGGC  CAGGGcGCGGTATTGCaTgAcTaaTgTAcaATAA
33 7662 tgtacTtgctgcAttgacTCAtatataCatGCAGtgcaATtgcaaAaTaCTTaATTgtacTAatAgtT
16 7666 cacTaTgcgcCAACgcctTacatACcgCtgtTAGgcacATatTtTTggcTTgTtTTAactAACcTAAT
31 7657 tGtTtaaaTACAACtgtagttcaACtATgtgTcatgcAcaTATATTataTTaTCCTAcAcAcCTTAAA
18 7626 aGgTgcgcTACAAC             aATtgcTtgcatAacTATAT  ccactcCCTA AgtaaTaAAA

con     tg-tatg-tacaacgccatc-a-acaactgg-agca-aatt-tata-t-cttt-cta-a--actaaaa
                               BE31-XXAGGCACAXAXXXX-BE31 hpv16+18+33
    015-AGGTGCGCTACAAC         AATTGCTTGCATAACTATAT  CCACTCCCTA AGTAATAAAA-015
    024-CACTATGCGCCAACGCCTTACATACCGCTGTTAGGCACATATTTTGGCTTGTTTTAACTAACCTAAT-024


 6 7723 ACCTGTC  TTTGTgttAtAcTtTTaTGcAcTGtAGCCAActcTTAAAAGCATTTTTGGCTTgTAGCa
11 7753 ACCTGTCGgTTTGT   ACAaTgTTgTGgATTGCAGCCAAAggTTAAAAGCATTTTTGGCTTcTAGCt
33 7730 TaCAcATGcTTTtaggcACATAtTTTTactTTaCtttCAAAccTTAAgtGCAGTTTTGGCTT   aCa
16 7734 TgCATATTtGGCAtAaggTTTAaacTTcTAaggCcAaCtAAatgTcAccctAGTTCaTaCaTgaActg
31 7725 CTGCTTTTAGGCACATATTTT GTagaTTATctaTAtCctTgATTGCAgtgcTGGCTTtgcacAtgt
18 7680 CTGCTTTTAGGCACATATTTTaGTttgTTtTtacTtaagcTaATTGCAtactTGGCTT

con     --c-tttta---atataat-tagtttt-tattgct--caaa--tTaaa-gcattt-t-gcttgtagc-
             BE31-XXAGGCACAXAXXXX-BE31 hpv16+18+33
             BE31-XXAGGCACAXAXXXX-BE31 hpv16+18+33
    015-CTGCTTTTAGGCACATATTTTAGTTTGTTTTTACTTAAGCTAATTGCATACTTGGCTT-(015)
    024-TGCATATTTGGCATAAGGTTTAAACTTCTAAGGCCAACTAAATGTCACCCTAGTTCATACATGAACTG-024


 6 7789 GcACATTTTTtTgCtCTTAcTgTtTggTatACAATAaCataAAAATGAGTAACCTAAGGTCACACACC
11 7818 GAACATTTTTGTACcCTTAgTaTaTtaTgcACAATAcCcacAAAATGAGTAACCTAAGGTCACACACC
33 7795 cAAttgcTTTGTAtgCcaAactaTgccTTGTAAAAgtgagtcActacctgttTaTtAccaGGTGTGga
16 7802 TgtAAagGTTAgtcaTacATtgTTCATTTGTAAAA                    cTgcAcatgGGTGTGtg
31 7792 TtaAActGccAaggTTgtgTcaTgCATTaTaAATAagttgTatgttactcaTATAATtaATtgCatAt
18 7738     gtacaactacTTtcaTgtccaAcatTctgTctacccTtaacatgaacTATAAT  ATgaCtaAg

con     -aa-atttttt-tact-ttatt-tt-a-tttaaaaaaac-gtaaa-tg--tat--taagga-g--ta--
    015-    GTACAACTACTTTCATGTCCAACATTCTGTCTACCCTTAACATGAACTATAAT  ATGACTAAG-015
    024-TGTAAAGGTTAGTCATACATTGTTCATTTGTAAAA                    CTGCACATGGGTGTGTG-024
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 6 7857 TGCgACCGGTTTCGGTTAtCCACACCCTACATATTTCCTTCTTATA
11 7886 TGCAACCGGTTTCGGTTAcCCACACCCTACATATTTCCTTCTTATA
33 7863 CtAACCG TTTTaGGTcAtaTTggtCATTTA tAaTCtTTTATATAATA
16 7854 CaAACCGATTTT     gGGTTACACATTTACAAGCAAcTTATATAATAATACTaa
31 7860 agGTattAcaccgtTTTcGGTTACAGtTTTACAAGCAAtTGtTCTTtTTATACT
18 7800 ctGTgcatacatagTTTatGcaACcGaaaTAggttgggcaGcaCaTacTATACTtttc

con     cg-aac---ttt-ggttatg--acccat-tA-a-ttc-tt-ttataataatact----
     015-CTGTGCATACATAGTTTATGCAACCGAAATAGGTTGGGCAGCACATACTATACTTTTC-(015)
     024-CAAACCGATTTT     GGGTTACACATTTACAAGCAACTTATATAATAATACTAA(-024)
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Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, GR, IT, NL, SE

1. A composition useful in LCR for amplifying the DNA of human papilloma virus present in a test sample, said composition comprising a set of four oligonucleotide probes, said probe sets being selected from the group consisting of the following oligonucleotide sets:

LCR5: SEQ ID No.

81	GCTGCAAACA ACTATACATG ATATAA,
82	TTATATCATG TATAGTTGTT TGCAGC,
83	TATTAGAATG TGTGTACTGC AAGCA,
84	TGCTTGCAGT ACACACATTC TAATA;

LCR6: SEQ ID No.

85	CTTCACTGCA AGACATAGAA ATAA,
86	TTATTTCTAT GTCTTGCAGT GAA,
87	CCTGTGTATA TTGCAAGACA GTAT,
88	TACTGTCTTG CAATATACAC AGG;

LCR7: SEQ ID No.

89	TATATTGCAA GACAGTATTG GAAC,
90	GTTCCAATAC TGTCTTGCAA TTTA,
91	TTACAGAGGT ATTTGAATTT GCATT,
92	AATGCAAATT CAAATACCTC TGTAA; and

LCR8: SEQ ID No.

93	GTATGGAACA ACATTAGAAC AGCA,
94	TGCTGTTCTA ATGTTGTTCC ATAC,
95	ATACAACAAA CCGTTGTGTG ATTT,
96	AAATCACACA ACGGTTTGTT GTAT.

2. A composition according to claim 1 for amplifying the DNA of human papilloma virus type 1 6 present in a test sample, said composition comprising a set of four oligonucleotide probes, said probe sets being selected from the group consisting of the following oligonucleotide sets:
LCR5 (SEQ ID Nos. 81,82,83 and 84) and LCR8 (SEQ ID Nos. 93, 94, 95 and 96).

3. A composition according to claim 1 for amplifying the DNA of human papilloma virus type 18 present in a test sample, said composition comprising a set of four oligonucleotide probes, said probe sets being selected from the group consisting of the following oligonucleotide sets:
LCR 6(SEQ ID Nos. 85,86,87 and 88) and LCR 7 (SEQ ID Nos. 89,90,91 and 92).

4. A kit for detecting the presence of human papilloma virus DNA in a test sample, comprising:
a composition according to any of claims 1 to 3; and
further comprising a ligase.

5. A kit according to claim 4, wherein said ligase is thermostable.

6. A composition useful in PCR for amplifying the DNA of human papilloma virus present in a test sample, said composition comprising:

a first nucleic acid primer of sense direction, capable of hybridizing to the antisense strand of HPV DNA , said primer having from 10 to about 30 nucleotides in length and having a sequence selected from the group consisting of the following sequences:

SEQ ID No.	
1	CAGATGTCTC TGTGGCGGCC TAGTG,
6	GAATTAGTTA GACCATTTAA AAG,
7	GGGGAAACAC CAGAATGGAT A,
81	GCTGCAAACA ACTATACATG ATATAA,
85	CTTCACTGCA AGACATAGAA ATAA,
89	TATATTGCAA GACAGTATTG GAAC and
93	GTATGGAACA ACATTAGAAC AGCA; and

a second nucleic acid primer of antisense direction, capable of hybridizing to the sense strand of HPV DNA, said primer having from 10 to about 30 nucleotides in length and-having a sequence selected from the group consisting of the following sequences:

SEQ ID No.	
5	AGGTGTCAGG AAAACCAAAT TTATT,
84	TGCTTGCAGT ACACACATTC TAATA,
88	TACTGTCTTG CAATATACAC AGG,
92	AATGCAAATT CAAATACCTC TGTAA and
96	AAATCACACA ACGGTTTGTT GTAT;

provided said first and second primers hybridize to their respective antisense and sense strands at locations such that their 3' ends do not overlap and, in the direction of extension, the 5' ends of said primers are spaced further apart than the 3' ends of said primers.

7. A composition according to claim 6 wherein said first and second primers are selected from the following pairs of oligonucleotide sequences (identified by Sequence ID No.):
1 and 5, 6 and 5, 7 and 5, 81 and 84,
85 and 88, 89 and 92, and 93 and 96.

8. A kit for detecting the presence of human papilloma virus DNA in a test sample, comprising:
a composition according to claim 6 or 7 ; and
further comprising a polymerase.

9. A kit according to claim 8 wherein said polymerase is thermostable.

10. A consensus oligonucleotide for hybridizing human papilloma virus types 6, 11, 16, 18, 31, 33 and 61, which oligonucleotide comprises from about 10 to about 60 nucleotides in length and is selected from the group of sequences consisting of:

SEQ ID No.	
1	CAGATGTCTC TGTGGCGGCC TAGTG,
5	AGGTGTCAGG AAAACCAAAT TTATT,
6	GAATTAGTTA GACCATTTAA AAG and
7	GGGGAAACAC CAGAATGGAT A;

and their complements.

11. A type-specific oligonucleotide for determining the presence of human papilloma virus type 16, having a sequence selected from the group consisting of:

SEQ ID No.	
81	GCTGCAAACA ACTATACATG ATATAA,
82	TTATATCATG TATAGTTGTT TGCAGC,
83	TATTAGAATG TGTGTACTGC AAGCA,
84	TGCTTGCAGT ACACACATTC TAATA,
93	GTATGGAACA ACATTAGAAC AGCA,
94	TGCTGTTCTA ATGTTGTTCC ATAC,
95	ATACAACAAA CCGTTGTGTG ATTT and
96	AAATCACACA ACGGTTTGTT GTAT;

and their complements.

12. A type-specific oligonucleotide for determining the presence of human papilloma virus type 18, having a sequence selected from the group consisting of: SEQ ID No.

SEQ ID No.	
85	CTTCACTGCA AGACATAGAA ATAA,
86	TTATTTCTAT GTCTTGCAGT GAA,
87	CCTGTGTATA TTGCAAGACA GTAT,
88	TACTGTCTTG CAATATACAC AGG,
89	TATATTGCAA GACAGTATTG GAAC,
90	GTTCCAATAC TGTCTTGCAA TTTA,
91	TTACAGAGGT ATTTGAATTT GCATT and
92	AATGCAAATT CAAATACCTC TGTAA;

and their complements.

13. A method for determining the presence of any human papilloma virus in a test sample, comprising:

a. hybridizing DNA in the test sample with at least one consensus oligonucleotide selected from the group of claim 10, said oligonucleotide being conjugated to a signal generating compound capable of producing a detectable signal; and
b. determining the presence of human papilloma virus by detecting the signal generated.

14. A method for determining the presence of human papilloma virus type 16 in a test sample, comprising:

a. hybridizing DNA in the test sample with at least one oligonucleotide selected from the group of claim 11, said oligonucleotide being conjugated to a signal generating compound capable of producing a detectable signal; and
b. determining the presence of human papilloma virus by detecting the signal generated.

15. A method for determining the presence of human papilloma virus type 18 in a test sample, comprising:

a. hybridizing DNA in the test sample with at least one oligonucleotide selected from the group of claim 12, said oligonucleotide being conjugated to a signal generating compound capable of producing a detectable signal; and
b. determining the presence of human papilloma virus by detecting the signal generated.

16. A method according to any of claims 13-15, further comprising a step of amplification prior to or concurrent with said hybridizing step.

17. A method according to claim 16, wherein said amplification step comprises PCR or LCR.

Claims for the following Contracting States : ES

1. A composition useful in LCR for amplifying the DNA of human papilloma virus present in a test sample, said composition comprising a set of four oligonucleotide probes, said probe sets being selected from the group consisting of the following oligonucleotide sets:

LCR5: SEQ ID No.
81 GCTGCAAACA ACTATACATG ATATAA,
82 TTATATCATG TATAGTTGTT TGCAGC,
83 TATTAGAATG TGTGTACTGC AAGCA,
84 TGCTTGCAGT ACACACATTC TAATA;

LCR6: SEQ ID No.
85 CTTCACTGCA AGACATAGAA ATAA,
86 TTATTTCTAT GTCTTGCAGT GAA,
87 CCTGTGTATA TTGCAAGACA GTAT,
88 TACTGTCTTG CAATATACAC AGG;

LCR7: SEQ ID No.
89 TATATTGCAA GACAGTATTG GAAC,
90 GTTCCAATAC TGTCTTGCAA TTTA,
91 TTACAGAGGT ATTTGAATTT GCATT,
92 AATGCAAATT CAAATACCTC TGTAA; and

LCR8: SEQ ID No.
93 GTATGGAACA ACATTAGAAC AGCA,
94 TGCTGTTCTA ATGTTGTTCC ATAC,
95 ATACAACAAA CCGTTGTGTG ATTT,
96 AAATCACACA ACGGTTTGTT GTAT.

2. A composition according to claim 1 for amplifying the DNA of human papilloma virus type 16 present in a test sample, said composition comprising a set of four oligonucleotide probes, said probe sets being selected from the group consisting of the fol lowing oligonucleotide sets :
LCR5 (SEQ ID Nos. 81,82,83 and 84) and LCR8 (SEQ ID Nos. 93, 94, 95 and 96).

3. A composition according to claim 1 for amplifying the DNA of human papilloma virus type 18 present in a test sample, said composition comprising a set of four oligonucleotide probes, said probe sets being selected from the group consisting of the following oligonucleotide sets:
LCR6(SEQ ID Nos. 85,86,87 and 88) and LCR 7(SEQ ID Nos. 89,90,91 and 92).

4. A kit for detecting the presence of human papilloma virus DNA in a test sample, comprising:

a composition according to any of claims 1 to 3; and further comprising a ligase.

5. A kit according to claim 4, wherein said ligase is thermostable.

6. A composition useful in PCR for amplifying the DNA of human papilloma virus present in a test sample, said composition comprising:

a first nucleic acid primer of sense direction, capable of hybridizing to the antisense strand of HPV DNA, said primer having from 10 to about 30 nucleotides in length and having a sequence selected from the group consisting of the following sequences:

SEQ ID No.	
1	CAGATGTCTC TGTGGCGGCC TAGTG,
6	GAATTAGTTA GACCATTTAA AAG,
7	GGGGAAACAC CAGAATGGAT A,
81	GCTGCAAACA ACTATACATG ATATAA,
85	CTTCACTGCA AGACATAGAA ATAA,
89	TATATTGCAA GACAGTATTG GAAC and
93	GTATGGAACA ACATTAGAAC AGCA; and

a second nucleic acid primer of antisense direction, capable of hybridizing to the sense strand of HPV DNA, said primer having from 10 to about 30 nucleotides in length and having a sequence selected from the group consisting of the following sequences:

SEQ ID No.	
5	AGGTGTCAGG AAAACCAAAT TTATT,
84	TGCTTGCAGT ACACACATTC TAATA,
88	TACTGTCTTG CAATATACAC AGG,
92	AATGCAAATT CAAATACCTC TGTAA and
96	AAATCACACA ACGGTTTGTT GTAT;

provided said first and second primers hybridize to their respective antisense and sense strands at locations such that their 3' ends do not overlap and, in the direction of extension, the 5' ends of said primers are spaced further apart than the 3' ends of said primers.

7. A composition according to claim 6 wherein said first and second primers are selected from the following pairs of oligonucleotide sequences (identified by Sequence ID No.):
1 and 5, 6 and 5, 7 and 5, 81 and 84,
85 and 88, 89 and 92, and 93 and 96.

8. A kit for detecting the presence of human papilloma virus DNA in a test sample, comprising:
a composition according to claim 6 or 7; and
further comprising a polymerase.

9. A kit according to claim 8 wherein said polymerase is thermostable.

10. A method for determining the presence of any human papilloma virus in a test sample, comprising:

a. hybridizing DNA in the test sample with at least one consensus oligonucleotide selected from the group of sequences consisting of:

SEQ ID No.

1	CAGATGTCTC TGTGGCGGCC TAGTG,
5	AGGTGTCAGG AAAACCAAAT TTATT,
6	GAATTAGTTA GACCATTTAA AAG and
7	GGGGAAACAC CAGAATGGAT A;

and their complements,
said oligonucleotide being conjugated to a signal generating compound capable of producing a detectable signal; and
b. determining the presence of human papilloma virus by detecting the signal generated.

11. . A method for determining the presence of human papilloma virus type 16 in a test sample, comprising:

a. hybridizing DNA in the test sample with at least one oligonucleotide selected from the group of sequences consisting of:

SEQ ID No.

81	GCTGCAAACA ACTATACATG ATATAA,
82	TTATATCATG TATAGTTGTT TGCAGC,
83	TATTAGAATG TGTGTACTGC AAGCA,
84	TGCTTGCAGT ACACACATTC TAATA,
93	GTATGGAACA ACATTAGAAC AGCA,
94	TGCTGTTCTA ATGTTGTTCC ATAC,
95	ATACAACAAA CCGTTGTGTG ATTT and
96	AAATCACACA ACGGTTTGTT GTAT;

and their complements, said oligonucleotide being conjugated to a signal generating compound capable of producing a detectable signal; and
b. determining the presence of human papilloma virus by detecting the signal generated.

12. . A method for determining the presence of human papilloma virus type 18 in a test sample, comprising:

a. hybridizing DNA in the test sample with at least one oligonucleotide selected from the group of sequences consisting of:

SEQ ID No

85	CTTCACTGCA AGACATAGAA ATAA,
86	TTATTTCTAT GTCTTGCAGT GAA,
87	CCTGTGTATA TTGCAAGACA GTAT,
88	TACTGTCTTG CAATATACAC AGG,
89	TATATTGCAA GACAGTATTG GAAC,
90	GTTCCAATAC TGTCTTGCAA TTTA,
91	TTACAGAGGT ATTTGAATTT GCATT and
92	AATGCAAATT CAAATACCTC TGTAA;

and their complements,
said oligonucleotide being conjugated to a signal generating compound capable of producing a detectable signal; and
b. determining the presence of human papilloma virus by detecting the signal generated.

13. A method according to any of claims 10-12 , further comprising a step of amplification prior to or concurrent with said hybridizing step.

14. A method according to claim 13, wherein said amplification step comprises PCR or LCR.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, DK, FR, GB, GR, IT, NL, SE

1. Zusammensetzung, die für die LCR ("ligase chain reaction", Ligasekettenreaktion) zur Vervielfachung der DNA des humanen Papillomavirus nützlich ist, der in einer Testprobe vorhanden ist, wobei die Zusammensetzung einen Satz von vier Oligonukleotidsonden umfaßt, wobei die Sondensätze aus der Gruppe gewählt sind, die aus den folgenden Oligonukleotidsätzen besteht:

LCR5:	SEQ ID Nr	
	81	GCTGCAAACA ACTATACATG ATATAA,
	82	TTATATCATG TATAGTTGTT TGCAGC,
	83	TATTAGAATG TGTGTACTGC AAGCA,
	84	TGCTTGCAGT ACACACATTC TAATA;
LCR6:	SEQ ID Nr	
	85	CTTCACTGCA AGACATAGAA ATAA,
	86	TTATTTCTAT GTCTTGCAGT GAA,
	87	CCTGTGTATA TTGCAAGACA GTAT,
	88	TACTGTCTTG CAATATACAC AGG;
LCR7:	SEQ ID Nr	
	89	TATATTGCAA GACAGTATTG GAAC,
	90	GTTCCAATAC TGTCTTGCAA TTTA,
	91	TTACAGAGGT ATTTGAATTT GCATT,
	92	AATGCAAATT CAAATACCTC TGTAA; und
LCR8:	SEQ ID Nr	
	93	GTATGGAACA ACATTAGAAC AGCA,
	94	TGCTGTTCTA ATGTTGTTCC ATAC,
	95	ATACAACAAA CCGTTGTGTG ATTT,
	96	AAATCACACA ACGGTTTGTT GTAT.

2. Zusammensetzung nach Anspruch 1 zur Vervielfachung der DNA des humanen Papillomavirus Typ 16, der in einer Testprobe vorhanden ist, wobei die Zusammensetzung einen Satz von vier Oligonukleotidsonden umfaßt, wobei die Sondensätze aus der Gruppe gewählt sind, die aus den folgenden Oligonukleotidsätzen besteht: LCR5 (SEQ ID Nrn 81, 82, 83 und 84) und LCR8 (SEQ ID Nm 93, 94, 95 und 96)

3. Zusammensetzung nach Anspruch 1 zur Vervielfachung der DNA des humanen Papillomavirus Typ 18, der in einer Testprobe vorhanden ist, wobei die Zusammensetzung einen Satz von vier Oligonukleotidsonden umfaßt, wobei die Sondensätze aus der Gruppe gewählt sind, die aus den folgenden Oligonukleotidsätzen besteht: LCR6 (SEQ ID Nrn 85, 86, 87 und 88) und LCR7 (SEQ ID Nrn 89, 90, 91 und 92).

4. Kit zum Nachweis der Anwesenheit der DNA des humanen Papillomavirus in einer Testprobe, das folgendes umfaßt:
eine Zusammensetzung nach einem der Ansprüche 1 bis 3, und des weiteren eine Ligase.

5. Kit nach Anspruch 4, worin die Ligase thermostabil ist.

6. Zusammensetzung, die bei der PCR ("polymerase chain reaction" Polymerasekettenreaktion) zur Vervielfachung der DNA des humanen Papillomavirus nützlich ist, der in einer Testprobe vorhanden ist, wobei die Zusammensetzung folgendes umfaßt:

einen ersten Nukleinsäureprimer, der zur Richtung gleichläufig ist, welcher zur Hybridisierung an den gegenläufigen Strang der HPV-DNA befähigt ist, wobei der Primer 10 bis ungefähr 30 Nukleotide lang ist und eine Sequenz aufweist, die aus der Gruppe gewählt ist, die aus den folgenden Sequenzen besteht:

```
1     CAGATGTCTC  TGTGGCGGCC  TAGTG,

6     GAATTAGTTA  GACCATTTAA  AAG,
7     GGGGAAACAC  CAGAATGGAT  A,

81    GCTGCAAACA  ACTATACATG  ATATAA,
85    CTTCACTGCA  AGACATAGAA  ATAA,
89    TATATTGCAA  GACAGTATTG  GAAC  und
93    GTATGGAACA  ACATTAGAAC  AGCA; und
```

einen zweiten Nukleinsäureprimer, der zur Richtung gegenläufig ist, welcher zur Hybridisierung an den gleichläufigen Strang der HPV-DNA befähigt ist, wobei der Primer 10 bis ungefähr 30 Nukleotide lang ist und eine Sequenz aufweist, die aus der Gruppe gewählt ist, die aus den folgenden Sequenzen besteht:

<u>SEQ ID Nr</u>

```
5     AGGTGTCAGG  AAAACCAAAT  TTATT,

84    TGCTTGCAGT  ACACACATTC  TAATA,
88    TACTGTCTTG  CAATATACAC  AGG,
92    AATGCAAATT  CAAATACCTC  TGTAA  und
96    AAATCACACA  ACGGTTTGTT  GTAT;
```

vorausgesetzt, daß der erste und der zweite Primer an ihre jeweiligen gleich- und gegenläufigen Stränge an solchen Stellen hybridisieren, daß ihre 3'-Enden nicht überlappen, und daß die 5'-Enden der Primer in Verlängerungsrichtung weiter räumlich abgesetzt sind als die 3'-Enden der Primer.

7. Zusammensetzung nach Anspruch 6, worin der erste und zweite Primer aus den folgenden Paaren von Oligonukleotidsequenzen (die durch die Sequenz ID Nr bezeichnet sind) gewählt sind:
1 und 5, 6 und 5, 7 und 5, 81 und 84,
85 und 88, 89 und 92, und 93 und 96.

8. Kit zum Nachweis der Anwesenheit der DNA des humanen Papillomavirus in einer Testprobe, das folgendes umfaßt:
eine Zusammensetzung nach Anspruch 6 oder ,7 und des weiteren eine Polymerase.

9. Kit nach Anspruch 8, worin die Polymerase thermostabil ist.

10. Consensus-Oligonukleotid zur Hybridisierung der humanen papillomaviren Typ 6, 11, 16, 18, 31, 33 und 61, wobei das Oligonukleotid ungefähr 10 bis ungefähr 60 Oligonukleotide lang ist und aus der Gruppe von Sequenzen gewählt ist, die aus folgendem besteht:

<u>SEQ ID Nr</u>

```
1     CAGATGTCTC  TGTGGCGGCC  TAGTG,
5     AGGTGTCAGG  AAAACCAAAT  TTATT,
6     GAATTAGTTA  GACCATTTAA  AAG
7     GGGGAAACAC  CAGAATGGAT  A;  und
```

und aus deren Komplementen.

11. Typ-spezifisches Oligonukleotid zur Bestimmung der Anwesenheit des humanen Papillomavirus Typ 16, das eine Sequenz aufweist, die aus der Gruppe gewählt ist, die aus folgendem besteht:

SEQ ID Nr			
81	GCTGCAAACA	ACTATACATG	ATATAA,
82	TTATATCATG	TATAGTTGTT	TGCAGC,
83	TATTAGAATG	TGTGTACTGC	AAGCA,
84	TGCTTGCAGT	ACACACATTC	TAATA,
93	GTATGGAACA	ACATTAGAAC	AGCA,
94	TGCTGTTCTA	ATGTTGTTCC	ATAC,
95	ATACAACAAA	CCGTTGTGTG	ATTT und
96	AAATCACACA	ACGGTTTGTT	GTAT;

und aus deren Komplementen.

12. Typ-spezifisches Oligonukleotid zur Bestimmung der Anwesenheit des humanen Papillomavirus Typ 18, das eine Sequenz aufweist, die aus der Gruppe gewählt ist, die aus folgendem besteht:

SEQ ID Nr			
85	CTTCACTGCA	AGACATAGAA	ATAA,
86	TTATTTCTAT	GTCTTGCAGT	GAA,
87	CCTGTGTATA	TTGCAAGACA	GTAT,
88	TACTGTCTTG	CAATATACAC	AGG,
89	TATATTGCAA	GACAGTATTG	GAAC,
90	GTTCCAATAC	TGTCTTGCAA	TTTA,
91	TTACAGAGGT	ATTTGAATTT	GCATT und
92	AATGCAAATT	CAAATACCTC	TGTAA;

und aus deren Komplementen.

13. Verfahren zur Bestimmung der Anwesenheit irgendeines humanen Papillomavirus in einer Testprobe, das folgendes umfaßt:

a. Hybridisieren der DNA in der Testprobe mit wenigstens einem Consensus-Oligonukleotid, das aus der Gruppe nach Anspruch 10 gewählt ist, wobei das Oligonukleotid an eine signalerzeugende Verbindung konjugiert ist, die zur Erzeugung eines nachweisbaren Signals befähigt ist, und
b. Bestimmen der Anwesenheit des humanen Papillomavirus, indem das erzeugte Signal nachgewiesen wird.

14. Verfahren zur Bestimmung der Anwesenheit des humanen Papillomavirus Typ 16 in einer Probe, das folgendes umfaßt:

a. Hybridisieren der DNA in der Testprobe mit wenigstens einem Oligonukleotid, das aus der Gruppe nach Anspruch 11 gewählt ist, wobei das Oligonukleotid an eine signalerzeugende Verbindung konjugiert ist, die zur Erzeugung eines nachweisbaren Signals befähigt ist, und
b. Bestimmen der Anwesenheit des humanen Papillomavirus, indem das erzeugte Signal nachgewiesen wird.

15. Verfahren zur Bestimmung der Anwesenheit des humanen Papillomavirus Typ 18 in einer Testprobe, das folgendes umfaßt:

a. Hybridisieren der DNA in der Testprobe mit wenigstens einem Oligonukleotid, das aus der Gruppe nach Anspruch 12 gewählt ist, wobei das Oligonukleotid an eine signalerzeugende Verbindung konjugiert ist, die zur Erzeugung eines nachweisbaren Signals befähigt ist, und

b. Bestimmen der Anwesenheit des humanen Papillomavirus, indem das erzeugte Signal nachgewiesen wird.

16. Verfahren nach einem der Ansprüche 13-15, das des weiteren einen Vervielfachungsschritt umfaßt, der vor oder in Konkurrenz mit dem Hybridisierungsschritt stattfindet.

17. Verfahren nach Anspruch 16, worin der Vervielfachungsschritt PCR oder LCR umfaßt.

Patentansprüche für folgenden Vertragsstaat : ES

1. Zusammensetzung, die für die LCR ("ligase chain reaction", Ligasekettenreaktion) zur Vervielfachung der DNA des humanen Papillomavirus nützlich ist, der in einer Testprobe vorhanden ist, wobei die Zusammensetzung einen Satz von vier Oligonukleotidsonden umfaßt, wobei die Sondensätze aus der Gruppe gewählt sind, die aus den folgenden Oligonukleotidsätzen besteht:

LCR5: SEQ ID Nr
81 GCTGCAAACA ACTATACATG ATATAA,
82 TTATATCATG TATAGTTGTT TGCAGC,
83 TATTAGAATG TGTGTACTGC AAGCA,
84 TGCTTGCAGT ACACACATTC TAATA;

LCR6: SEQ ID Nr
85 CTTCACTGCA AGACATAGAA ATAA,
86 TTATTTCTAT GTCTTGCAGT GAA,
87 CCTGTGTATA TTGCAAGACA GTAT,
88 TACTGTCTTG CAATATACAC AGG;

LCR7: SEQ ID Nr
89 TATATTGCAA GACAGTATTG GAAC,
90 GTTCCAATAC TGTCTTGCAA TTTA,
91 TTACAGAGGT ATTTGAATTT GCATT,
92 AATGCAAATT CAAATACCTC TGTAA;

LCR8: SEQ ID Nr
93 GTATGGAACA ACATTAGAAC AGCA, und
94 TGCTGTTCTA ATGTTGTTCC ATAC,
95 ATACAACAAA CCGTTGTGTG ATTT,
96 AAATCACACA ACGGTTTGTT GTAT.

2. Zusammensetzung nach Anspruch 1 zur Vervielfachung der DNA des humanen Papillomavirus Typ 16, der in einer Testprobe vorhanden ist, wobei die Zusammensetzung einen Satz von vier Oligonukleotidsonden umfaßt, wobei die Sondensätze aus der Gruppe gewählt sind, die aus den folgenden Oligonukleotidsätzen besteht: LCR5 (SEQ ID Nrn 81, 82, 83 und 84) und LCR8 (SEQ ID Nrn 93, 94, 95 und 96).

3. Zusammensetzung nach Anspruch 1 zur Vervielfachung der DNA des humanen Papillomavirus TYP 18, der in einer Testprobe vorhanden ist, wobei die Zusammensetzung einen Satz von vier Oligonukleotidsonden umfaßt, wobei die Sondensätze aus der Gruppe gewählt sind, die aus den folgenden Oligonukleotidsätzen besteht: LCR6 (SEQ ID Nrn 85, 86, 87 und 88) und LCR7 (SEQ ID Nrn 89, 90, 91 und 92).

4. Kit zum Nachweis der Anwesenheit der DNA des humanen Papillomavirus in einer Testprobe, das folgendes umfaßt:
eine Zusammensetzung nach einem der Ansprüche 1 bis 3, und des weiteren eine Ligase.

5. Kit nach Anspruch 4, worin die Ligase thermostabil ist.

6. Zusammensetzung, die bei der PCR ("polymerase chain reaction" polymerasekettenreaktion) zur Vervielfachung der DNA des humanen Papillomavirus nützlich ist, der in einer Testprobe vorhanden ist, wobei die Zusammensetzung folgendes umfaßt:

   einen ersten Nukleinsäureprimer, der zur Richtung gleichläufig ist, welcher zur Hybridisierung an den gegenläufigen Strang der HPV-DNA befähigt ist, wobei der Primer 10 bis ungefähr 30 Nukleotide lang ist und eine Sequenz aufweist, die aus der Gruppe gewählt ist, die aus den folgenden Sequenzen besteht:

   SEQ ID Nr

1	CAGATGTCTC TGTGGCGGCC TAGTG,
6	GAATTAGTTA GACCATTTAA AAG,
7	GGGGAAACAC CAGAATGGAT A,
81	GCTGCAAACA ACTATACATG ATATAA,
85	CTTCACTGCA AGACATAGAA ATAA,
89	TATATTGCAA GACAGTATTG GAAC und
93	GTATGGAACA ACATTAGAAC AGCA; und

   einen zweiten Nukleinsäureprimer, der zur Richtung gegenläufig ist, welcher zur Hybridisierung an den gleichläufigen Strang der HPV-DNA befähigt ist, wobei der Primer 10 bis ungefähr 30 Nukleotide lang ist und eine Sequenz aufweist, die aus der Gruppe gewählt ist, die aus den folgenden Sequenzen besteht:

   SEQ ID Nr

5	AGGTGTCAGG AAAACCAAAT TTATT,
84	TGCTTGCAGT ACACACATTC TAATA,
88	TACTGTCTTG CAATATACAC AGG,
92	AATGCAAATT CAAATACCTC TGTAA und
96	AAATCACACA ACGGTTTGTT GTAT;

   vorausgesetzt, daß der erste und der zweite Primer an ihre jeweiligen gleich- und gegenläufigen Stränge an solchen Stellen hybridisieren, daß ihre 3'-Enden nicht überlappen, und daß die 5'-Enden der Primer in Verlängerungsrichtung weiter räumlich abgesetzt sind als die 3'-Enden der Primer.

7. Zusammensetzung nach Anspruch 6, worin der erste und zweite Primer aus den folgenden Paaren von Oligonukleotidsequenzen (die durch die Sequenz ID Nr bezeichnet sind) gewählt sind:
   1 und 5, 6 und 5, 7 und 5, 81 und 84,
   85 und 88, 89 und 92, und 93 und 96.

8. Kit zum Nachweis der Anwesenheit der DNA des humanen Papillomavirus in einer Testprobe, das folgendes umfaßt:

   eine Zusammensetzung nach Anspruch 6 oder 7, und des weiteren eine Polymerase.

9. Kit nach Anspruch 8, worin die Polymerase thermostabil ist.

10. Verfahren zur Bestimmung der Anwesenheit irgendeines humanen papillomavirus in einer Testprobe, das folgendes umfaßt:

    a. Hybridisieren der DNA in der Testprobe mit wenigstens einem Consensus-Oligonukleotid, das aus der Gruppe von Sequenzen gewählt ist, die aus folgendem besteht:

SEQ ID Nr

1	CAGATGTCTC TGTGGCGGCC TAGTG,
5	AGGTGTCAGG AAAACCAAAT TTATT
6	GAATTAGTTA GACCATTTAA AAG und
7	GGGGAAACAC CAGAATGGAT A;

und aus deren Komplementen,
wobei das Oligonukleotid an eine signalerzeugende Verbindung konjugiert ist, die zur Erzeugung eines nachweisbaren Signals befähigt ist, und
b. Bestimmen der Anwesenheit des humanen Papillomavirus, indem das erzeugte Signal nachgewiesen wird.

11. Verfahren zur Bestimmung der Anwesenheit des humanen Papillomavirus Typ 16 in einer Probe, das folgendes umfaßt:

a. Hybridisieren der DNA in der Testprobe mit wenigstens einem Oligonukleotid, das aus der Gruppe von Sequenzen gewählt ist, die aus folgendem besteht:

SEQ ID Nr

81	GCTGCAAACA ACTATACATG ATATAA,
82	TTATATCATG TATAGTTGTT TGCAGC,
83	TATTAGAATG TGTGTACTGC AAGCA,
84	TGCTTGCAGT ACACACATTC TAATA,
93	GTATGGAACA ACATTAGAAC AGCA,
94	TGCTGTTCTA ATGTTGTTCC ATAC,
95	ATACAACAAA CCGTTGTGTG ATTT und
96	AAATCACACA ACGGTTTGTT GTAT;

und aus deren Komplementen,
wobei das Oligonukleotid an eine signalerzeugende Verbindung konjugiert ist, die zur Erzeugung eines nachweisbaren Signals befähigt ist, und
b. Bestimmen der Anwesenheit des humanen Papillomavirus, indem das erzeugte Signal nachgewiesen wird.

12. Verfahren zur Bestimmung der Anwesenheit des humanen Papillomavirus Typ 18 in einer Testprobe, das folgendes umfaßt:

a. Hybridisieren der DNA in der Testprobe mit wenigstens einem Oligonukleotid, das aus der Gruppe von Sequenzen gewählt ist, die aus folgendem besteht:

SEQ ID Nr			
85	CTTCACTGCA	AGACATAGAA	ATAA,
86	TTATTTCTAT	GTCTTGCAGT	GAA,
87	CCTGTGTATA	TTGCAAGACA	GTAT,
88	TACTGTCTTG	CAATATACAC	AGG,
89	TATATTGCAA	GACAGTATTG	GAAC,
90	GTTCCAATAC	TGTCTTGCAA	TTTA,
91	TTACAGAGGT	ATTTGAATTT	GCATT und
92	AATGCAAATT	CAAATACCTC	TGTAA;

und aus deren Komplementen,
wobei das Oligonukleotid an eine signalerzeugende Verbindung konjugiert ist, die zur Erzeugung eines nachweisbaren Signals befähigt ist, und
b. Bestimmen der Anwesenheit des humanen Papillomavirus, indem das erzeugte Signal nachgewiesen wird.

13. Verfahren nach einem der Ansprüche 10-12, das des weiteren einen Vervielfachungsschritt umfaßt, der vor oder in Konkurrenz mit dem Hybridisierungsschritt stattfindet.

14. Verfahren nach Anspruch 13, worin der vervielfachungsschritt PCR oder LCR umfaßt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, DK, FR, GB, GR, IT, NL, SE

1. Composition utile dans la LCR pour amplifier l'ADN de virus du papillome humain présent dans échantillon à doser, ladite composition comprenant un ensemble de quatre sondes oligonucléotidiques, lesdits ensembles de sondes étant sélectionnés dans le groupe constitué par les ensembles d'oligonucléotides suivants :

LCR5 : n° d'identification

81	GCTGCAAACA	ACTATACATG	ATATAA,
82	TTATATCATG	TATAGTTGTT	TGCAGC,
83	TATTAGAATG	TGTGTACTGC	AAGCA,
84	TGCTTGCAGT	ACACACATTC	TAATA ;

LCR6 : n° d'identification

85	CTTCACTGCA	AGACATAGAA	ATAA,
86	TTATTTCTAT	GTCTTGCAGT	GAA,
87	CCTGTGTATA	TTGCAAGACA	GTAT,
88	TACTGTCTTG	CAATATACAC	AGG ;

LCR7 :	n° d'identification	
	89	TATATTGCAA GACAGTATTG GAAC
	90	GTTCCAATAC TGTCTTGCAA TTTA,
	91	TTACAGAGGT ATTTGAATTT GCATT,
	92	AATGCAAATT CAAATACCTC TGTAA ; et

LCR8 :	n° d'identification	
	93	GTATGGAACA ACATTAGAAC AGCA,
	94	TGCTGTTCTA ATGTTGTTCC ATAC,
	95	ATACAACAAA CCGTTGTGTG ATTT,
	96	AAATCACACA ACGGTTTGTT GTAT.

2. Composition selon la revendication 1, destinée à amplifier l'ADN de virus du papillome humain de type 16 présent dans un échantillon à doser, ladite composition comprenant un ensemble de quatre sondes oligonucléotidiques, lesdits ensembles de sondes étant sélectionnés dans le groupe constitué par les ensembles d'oligonucléotides suivants :
LCR5 (n° d'identification 81, 82, 83 et 84) et LCR8 (n° d'identification 93, 94, 95 et 96).

3. Composition selon la revendication 1, destinée à amplifier l'ADN de virus du papillome humain de type 18 présent dans un échantillon à doser, ladite composition comprenant un ensemble de quatre sondes oligonucléotidiques, lesdits ensembles de sondes étant sélectionnés dans le groupe constitué par les ensembles d'oligonucléotides suivants :
LCR6 (n° d'identification 85, 86, 87 et 88) et LCR7 (n° d'identification 89, 90, 91 et 92).

4. Kit de détection de la présence d'ADN de virus du papillome humain dans un échantillon à doser, comprenant : une composition selon l'une quelconque des revendications 1 à 3, et en outre une ligase.

5. Kit selon la revendication 4, dans lequel ladite ligase est thermostable.

6. Composition utile dans la PCR pour amplifier l'ADN de virus du papillome humain présent dans un échantillon à doser, ladite composition comprenant :

   une première amorce d'acide nucléique de direction sens, capable de s'hybrider au brin antisens de l'ADN de HPV, ladite amorce ayant de 10 à environ 30 nucléotides de long et une séquence sélectionnée dans le groupe constitué par les séquences suivantes :

N° d'identification	
1	CAGATGTCTC TGTGGCGGCC TAGTG,
6	GAATTAGTTA GACCATTTAA AAG,
7	GGGGAAACAC CAGAATGGAT A,
81	GCTGCAAACA ACTATACATG ATATAA,
85	CTTCACTGCA AGACATAGAA ATAA,
89	TATATTGCAA GACAGTATTG GAAC et
93	GTATGGAACA ACATTAGAAC AGCA ; et

   une deuxième amorce d'acide nucléique de direction antisens, capable de s'hybrider au brin sens de l'ADN

de HPV, ladite amorce ayant de 10 à environ 30 nucléotides de long et une séquence sélectionnée dans le groupe constitué par les séquences suivantes :

N° d'identification	
5	AGGTGTCAGG AAAACCAAAT TTATT,
84	TGCTTGCAGT ACACACATTC TAATA,
88	TACTGTCTTG CAATATACAC AGG,
92	AATGCAAATT CAAATACCTC TGTAA et
96	AAATCACACA ACGGTTTGTT GTAT ;

pour autant que lesdites première et deuxième amorces s'hybrident à leurs brins respectifs antisens et sens à des emplacements tels que leurs extrémités 3' ne se chevauchent pas et que, dans la direction d'extension, les extrémités 5' desdites amorces soient plus espacées que les extrémités 3' desdites amorces.

7. Composition selon la revendication 6, dans laquelle lesdites première et deuxième amorces sont sélectionnées parmi les paires suivantes de séquences oligonucléotidiques (identifiées par leur numéro d'identification) :
1 et 5, 6 et 5, 7 et 5, 81 et 84,
85 et 88, 89 et 92, et 93 et 96.

8. Kit de détection de la présence d'ADN de virus du papillome humain dans un échantillon à doser, comprenant :
une composition selon la revendication 6 ou 7 et en outre une polymérase.

9. Kit selon la revendication 8, dans lequel ladite polymérase est thermostable.

10. Oligonucléotide consensus pour hybridation du virus du papillome humain des types 6, 11, 16, 18, 31, 33 et 61, lequel oligonucléotide a d'environ 10 à environ 60 nucléotides de long et est sélectionné dans le groupe de séquences constitué par :

N° d'identification	
1	CAGATGTCTC TGTGGCGGCC TAGTG,
5	AGGTGTCAGG AAAACCAAAT TTATT,
6	GAATTAGTTA GACCATTTAA AAG et
7	GGGGAAACAC CAGAATGGAT A ;

et leurs compléments.

11. Oligonucléotide spécifique d'un type, destiné à déterminer la présence du virus du papillome humain de type 16, ayant une séquence sélectionnée dans le groupe constitué par :

N° d'identification	
81	GCTGCAAACA ACTATACATG ATATAA,
82	TTATATCATG TATAGTTGTT TGCAGC,
83	TATTAGAATG TGTGTACTGC AAGCA,
84	TGCTTGCAGT ACACACATTC TAATA,
93	GTATGGAACA ACATTAGAAC AGCA,
94	TGCTGTTCTA ATGTTGTTCC ATAC,
95	ATACAACAAA CCGTTGTGTG ATTT et
96	AAATCACACA ACGGTTTGTT GTAT ;

et leurs compléments.

12. Oligonucléotide spécifique d'un type, destiné à déterminer la présence du virus du papillome humain de type 18, ayant une séquence sélectionnée dans le groupe constitué par :

N° d'identification			
85	CTTCACTGCA	AGACATAGAA	ATAA,
86	TTATTTCTAT	GTCTTGCAGT	GAA,
87	CCTGTGTATA	TTGCAAGACA	GTAT,
88	TACTGTCTTG	CAATATACAC	AGG,
89	TATATTGCAA	GACAGTATTG	GAAC,
90	GTTCCAATAC	TGTCTTGCAA	TTTA,
91	TTACAGAGGT	ATTTGAATTT	GCATT et
92	AATGCAAATT	CAAATACCTC	TGTAA ;

et leurs compléments.

13. Procédé de détermination de la présence d'un virus quelconque du papillome humain dans un échantillon à doser, comprenant :

    a. l'hybridation de l'ADN dans l'échantillon à doser avec au moins un oligonucléotide consensus sélectionné dans le groupe selon la revendication 10, ledit oligonucléotide étant conjugué à un composé émetteur d'un signal, capable de produire un signal détectable, et
    b. la détermination de la présence du virus du papillome humain par détection du signal émis.

14. Procédé de détermination de la présence du virus du papillome humain de type 16 dans un échantillon à doser, comprenant :

    a. l'hybridation de l'ADN dans l'échantillon à doser avec au moins un oligonucléotide sélectionné dans le groupe selon la revendication 11, ledit oligonucléotide étant conjugué à un composé émetteur d'un signal, capable de produire un signal détectable, et
    b. la détermination de la présence du virus du papillome humain par détection du signal émis.

15. Procédé de détermination de la présence du virus du papillome humain de type 18 dans un échantillon à doser, comprenant :

    a. l'hybridation de l'ADN dans l'échantillon à doser avec au moins un oligonucléotide sélectionné dans le groupe selon la revendication 12, ledit oligonucléotide étant conjugué à un composé émetteur d'un signal, capable de produire un signal détectable, et
    b. la détermination de la présence du virus du papillome humain par détection du signal émis.

16. Procédé selon une quelconque des revendications 13 à 15, comprenant en outre une étape d'amplification avant ou pendant ladite étape d'hybridation.

17. Procédé selon la revendication 16, dans lequel ladite étape d'amplification comprend la PCR ou la LCR.

Revendications pour l'Etat contractant suivant : ES

1. Composition utile dans la LCR pour amplifier l'ADN de virus du papillome humain présent dans échantillon à doser, ladite composition comprenant un ensemble de quatre sondes oligonucléotidiques, lesdits ensembles de sondes étant sélectionnés dans le groupe constitué par les ensembles d'oligonucléotides suivants :

LCR5 : n° d'identification			
81	GCTGCAAACA	ACTATACATG	ATATAA,
82	TTATATCATG	TATAGTTGTT	TGCAGC,
83	TATTAGAATG	TGTGTACTGC	AAGCA,
84	TGCTTGCAGT	ACACACATTC	TAATA ;

LCR6 : n° d'identification

85	CTTCACTGCA AGACATAGAA ATAA,
86	TTATTTCTAT GTCTTGCAGT GAA,
87	CCTGTGTATA TTGCAAGACA GTAT,
88	TACTGTCTTG CAATATACAC AGG ;

LCR7 : n° d'identification

89	TATATTGCAA GACAGTATTG GAAC
90	GTTCCAATAC TGTCTTGCAA TTTA,
91	TTACAGAGGT ATTTGAATTT GCATT,
92	AATGCAAATT CAAATACCTC TGTAA ; et

LCR8 : n° d'identification

93	GTATGGAACA ACATTAGAAC AGCA,
94	TGCTGTTCTA ATGTTGTTCC ATAC,
95	ATACAACAAA CCGTTGTGTG ATTT,
96	AAATCACACA ACGGTTTGTT GTAT.

2. Composition selon la revendication 1, destinée à amplifier l'ADN de virus du papillome humain de type 16 présent dans un échantillon à doser, ladite composition comprenant un ensemble de quatre sondes oligonucléotidiques, lesdits ensembles de sondes étant sélectionnés dans le groupe constitué par les ensembles d'oligonucléotides suivants :
LCR5 (n° d'identification 81, 82, 83 et 84) et LCR8 (n° d'identification 93, 94, 95 et 96).

3. Composition selon la revendication 1, destinée à amplifier l'ADN de virus du papillome humain de type 18 présent dans un échantillon à doser, ladite composition comprenant un ensemble de quatre sondes oligonucléotidiques, lesdits ensembles de sondes étant sélectionnés dans le groupe constitué par les ensembles d'oligonucléotides suivants :
LCR6 (n° d'identification 85, 86, 87 et 88) et LCR7 (n° d'identification 89, 90, 91 et 92).

4. Kit de détection de la présence d'ADN de virus du papillome humain dans un échantillon à doser, comprenant :
une composition selon l'une quelconque des revendications 1 à 3, et en outre une ligase.

5. Kit selon la revendication 4, dans lequel ladite ligase est thermostable.

6. Composition utile dans la PCR pour amplifier l'ADN de virus du papillome humain présent dans un échantillon à doser, ladite composition comprenant :

une première amorce d'acide nucléique de direction sens, capable de s'hybrider au brin antisens de l'ADN de HPV, ladite amorce ayant de 10 à environ 30 nucléotides de long et une séquence sélectionnée dans le groupe constitué par les séquences suivantes :

N° d'identification			
1	CAGATGTCTC	TGTGGCGGCC	TAGTG,
6	GAATTAGTTA	GACCATTTAA	AAG,
7	GGGGAAACAC	CAGAATGGAT	A,
81	GCTGCAAACA	ACTATACATG	ATATAA,
85	CTTCACTGCA	AGACATAGAA	ATAA,
89	TATATTGCAA	GACAGTATTG	GAAC et
93	GTATGGAACA	ACATTAGAAC	AGCA ; et

une deuxième amorce d'acide nucléique de direction antisens, capable de s'hybrider au brin sens de l'ADN de HPV, ladite amorce ayant de 10 à environ 30 nucléotides de long et une séquence sélectionnée dans le groupe constitué par les séquences suivantes :

N° d'identification			
5	AGGTGTCAGG	AAAACCAAAT	TTATT,
84	TGCTTGCAGT	ACACACATTC	TAATA,
88	TACTGTCTTG	CAATATACAC	AGG,
92	AATGCAAATT	CAAATACCTC	TGTAA et
96	AAATCACACA	ACGGTTTGTT	GTAT ;

pour autant que lesdites première et deuxième amorces s'hybrident à leurs brins respectifs antisens et sens à des emplacements tels que leurs extrémités 3' ne se chevauchent pas et que, dans la direction d'extension, les extrémités 5' desdites amorces soient plus espacées que les extrémités 3' desdites amorces.

7. Composition selon la revendication 6, dans laquelle lesdites première et deuxième amorces sont sélectionnées parmi les paires suivantes de séquences oligonucléotidiques (identifiées par leur numéro d'identification) :
1 et 5, 6 et 5, 7 et 5, 81 et 84,
85 et 88, 89 et 92, et 93 et 96.

8. Kit de détection de la présence d'ADN de virus du papillome humain dans un échantillon à doser, comprenant :
une composition selon la revendication 6 ou 7 et
en outre une polymérase.

9. Kit selon la revendication 8, dans lequel ladite polymérase est thermostable.

10. Procédé de détermination de la présence d'un virus quelconque du papillome humain dans un échantillon à doser, comprenant :

a. l'hybridation de l'ADN dans l'échantillon à doser avec au moins un oligonucléotide consensus sélectionné dans le groupe de séquences constitué par :

N° d'identification			
1	CAGATGTCTC	TGTGGCGGCC	TAGTG,
5	AGGTGTCAGG	AAAACCAAAT	TTATT,
6	GAATTAGTTA	GACCATTTAA	AAG et
7	GGGGAAACAC	CAGAATGGAT	A ;

et leurs compléments, ledit oligonucléotide étant conjugué à un composé émetteur d'un signal, capable de produire un signal détectable, et
b. la détermination de la présence du virus du papillome humain par détection du signal émis.

11. Procédé de détermination de la présence du virus du papillome humain de type 16 dans un échantillon à doser, comprenant :

a. l'hybridation de l'ADN dans l'échantillon à doser avec au moins un oligonucléotide sélectionné dans le groupe de séquences constitué par :

N° d'identification			
81	GCTGCAAACA	ACTATACATG	ATATAA,
82	TTATATCATG	TATAGTTGTT	TGCAGC,
83	TATTAGAATG	TGTGTACTGC	AAGCA,
84	TGCTTGCAGT	ACACACATTC	TAATA,
93	GTATGGAACA	ACATTAGAAC	AGCA,
94	TGCTGTTCTA	ATGTTGTTCC	ATAC,
95	ATACAACAAA	CCGTTGTGTG	ATTT et
96	AAATCACACA	ACGGTTTGTT	GTAT ;

et leurs compléments,
ledit oligonucléotide étant conjugué à un composé émetteur d'un signal, capable de produire un signal détectable, et
b. la détermination de la présence du virus du papillome humain par détection du signal émis.

12. Procédé de détermination de la présence du virus du papillome humain de type 18 dans un échantillon à doser, comprenant :

a. l'hybridation de l'ADN dans l'échantillon à doser avec au moins un oligonucléotide sélectionné dans le groupe de séquences constitué par :

N° d'identification			
85	CTTCACTGCA	AGACATAGAA	ATAA,
86	TTATTTCTAT	GTCTTGCAGT	GAA,
87	CCTGTGTATA	TTGCAAGACA	GTAT,
88	TACTGTCTTG	CAATATACAC	AGG,
89	TATATTGCAA	GACAGTATTG	GAAC,
90	GTTCCAATAC	TGTCTTGCAA	TTTA,
91	TTACAGAGGT	ATTTGAATTT	GCATT et
92	AATGCAAATT	CAAATACCTC	TGTAA ;

et leurs compléments,
ledit oligonucléotide étant conjugué à un composé émetteur d'un signal, capable de produire un signal détectable, et
b. la détermination de la présence du virus du papillome humain par détection du signal émis.

13. Procédé selon une quelconque des revendications 10 à 12, comprenant en outre une étape d'amplification avant ou pendant ladite étape d'hybridation.

14. Procédé selon la revendication 13, dans lequel ladite étape d'amplification comprend la PCR ou la LCR.

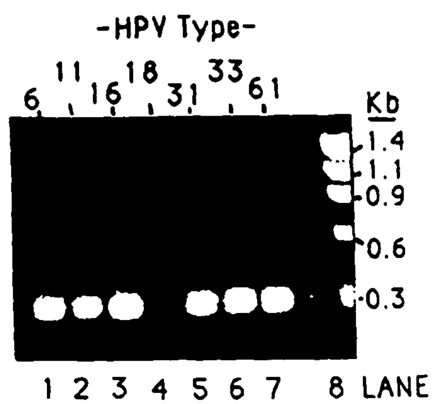

-HPV Type-
6
11
16
18
31
33
61
Kb
1.4
1.1
0.9
0.6
0.3
1 2 3 4 5 6 7 8 LANE

FIG. 1

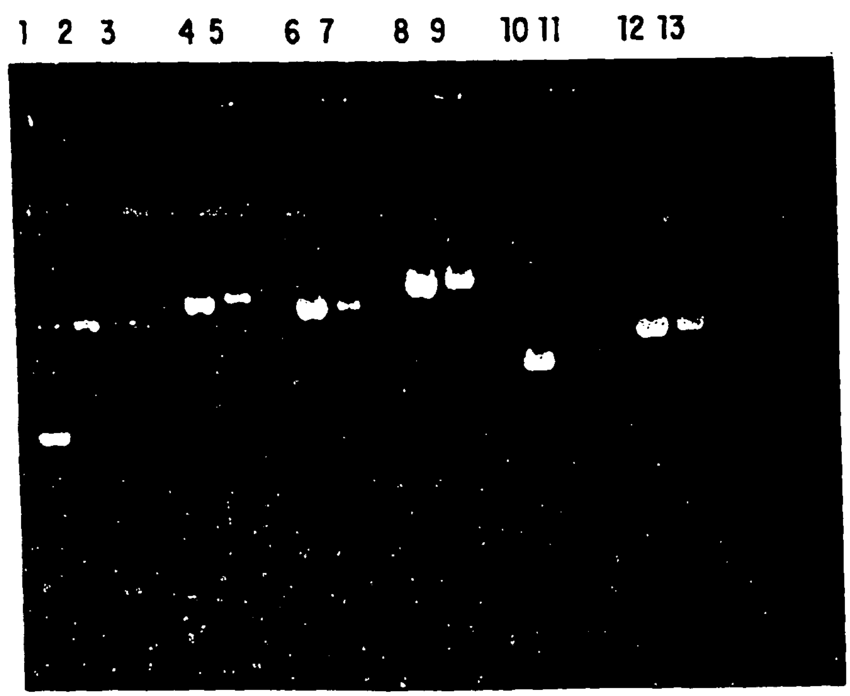

1 2 3 4 5 6 7 8 9 10 11 12 13

FIG. 2

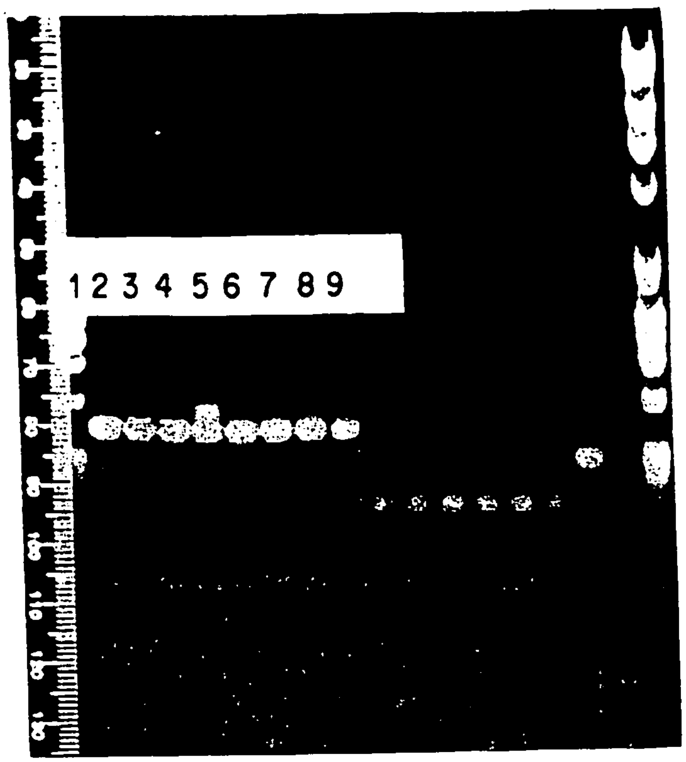


FIG. 3

FIG. 4

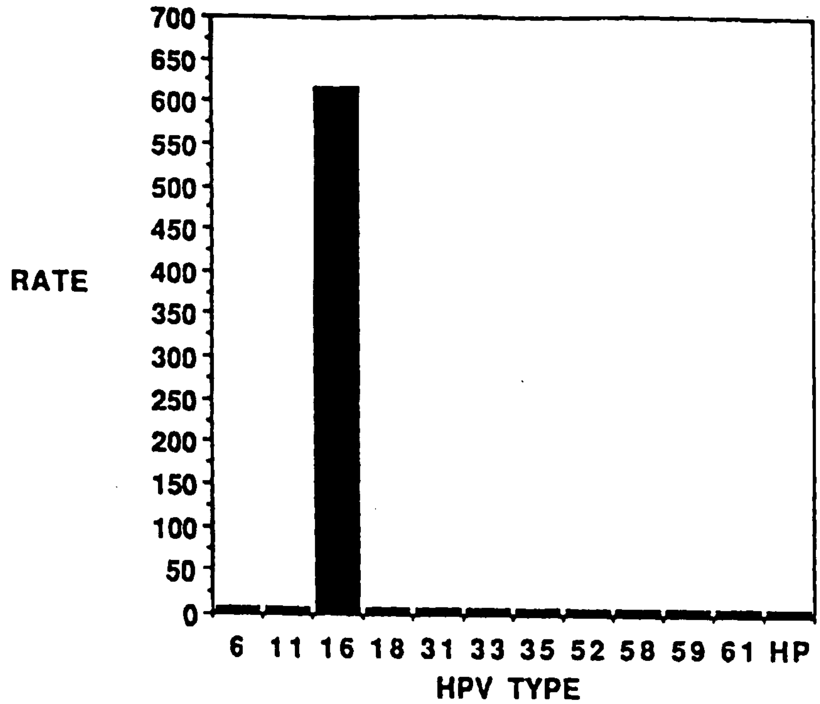
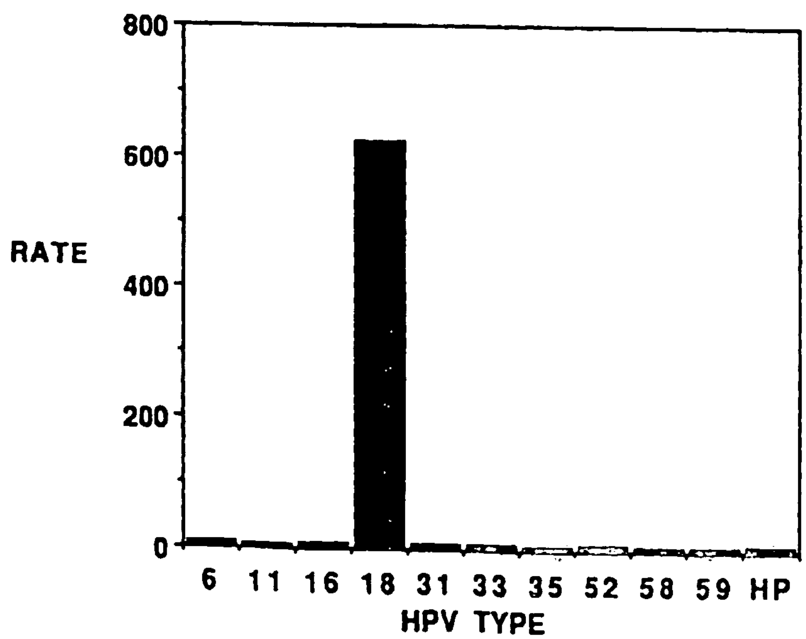

700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
RATE
6 11 16 18 31 33 35 52 58 59 61 HP
HPV TYPE

FIG. 5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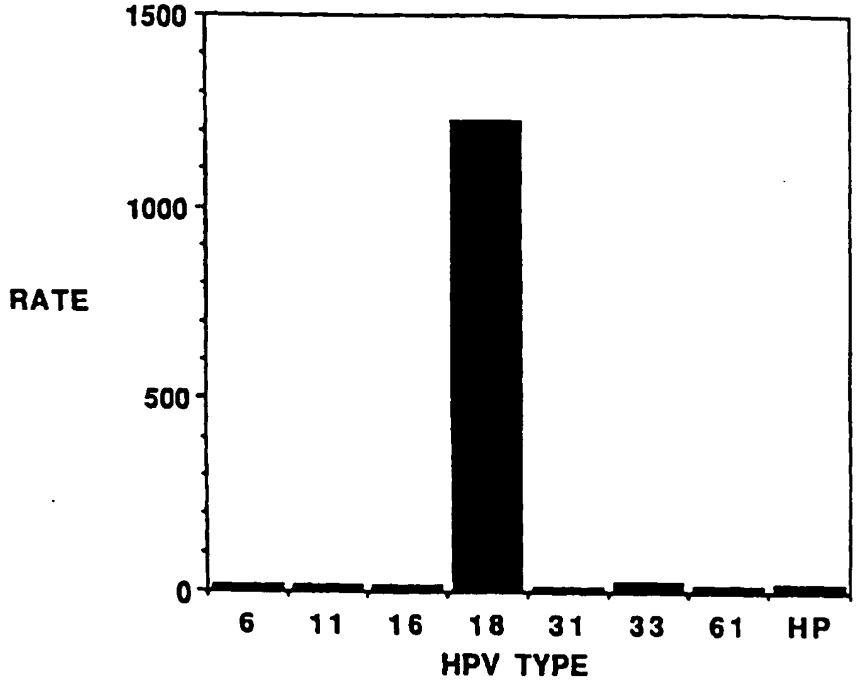
HPV TYPE

FIG. 6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RATE
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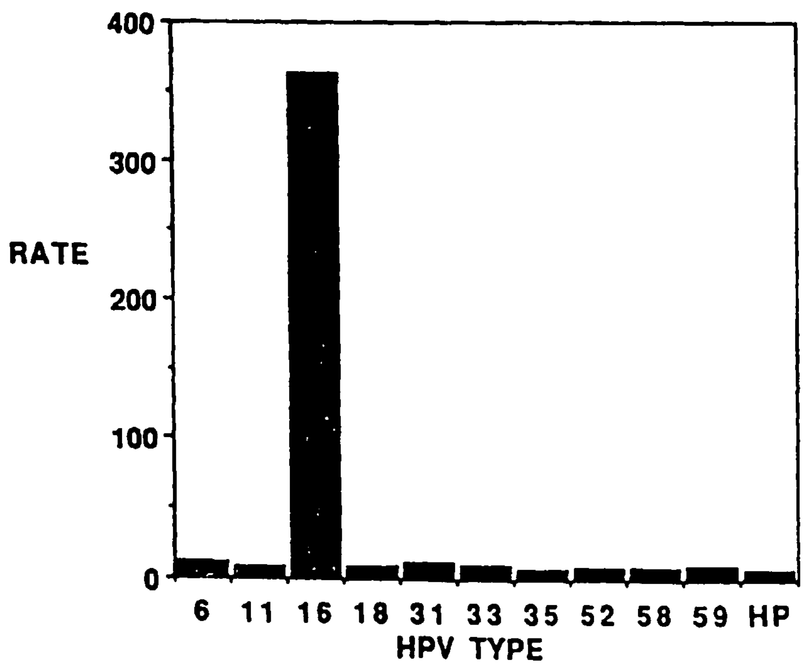
11
16
18
31
33
61
HP
HPV TYPE

FIG. 7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RATE
6
11
16
18
31
33
35
52
58
59
HP
HPV TYPE